The Reactions of Aromatic Compounds with Nitrogen Dioxide.

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Contents.

Abstract

In the first part of this thesis the reactions of 3,4,5-trimethylphenol (58), 3,4-dimethylphenol (71) and 4-methylphenol (88) with nitrogen dioxide in benzene, and in dichloromethane, are investigated. These phenols are unsubstituted at C2 and C6. Typically the products of the reaction are 2,6-dinitrophenols, and 4-nitro or 4-hydroxy cyclohexa-2,5-dienones. The mode of formation of these compounds is described.

In the second part of this thesis 3,4,5-trimethylbiphenyl (91) and 2,3,4-trimethylbiphenyl (92) were treated with nitrogen dioxide in benzene. Reaction of 3,4,5-trimethylbiphenyl (91) gave ring nitrated biphenyls [(97), (98) and (99)], nitromethylbiphenyl (100) and ring nitrated nitromethyl biphenyls [(101), (102) and (103)]. In contrast reaction of 2,3,4-trimethylbiphenyl (92) gave nitratomethylbiphenyls [(111), (112) and (113)] and ketones [(117) and (118)] in addition to the ring nitrated biphenyls [(114), (115) and (116)]. The mode of formation of these compounds is described.

In the third part of this thesis the reaction of phenanthrene (130) with nitrogen dioxide in benzene was carried out. This reaction gave the novel isomeric nitro nitrates [(135) and (136)] in addition to the dimeric nitro nitrate (132) and nitrophenanthrenes [(131), (133) and (134)]. An overall mechanistic scheme for the formation of these compound is proposed.

Throughout this thesis, extensive use is made of high field Fourier transform n.m.r. techniques and in three cases single crystal X-ray structure analyses were necessary for structure determinations.

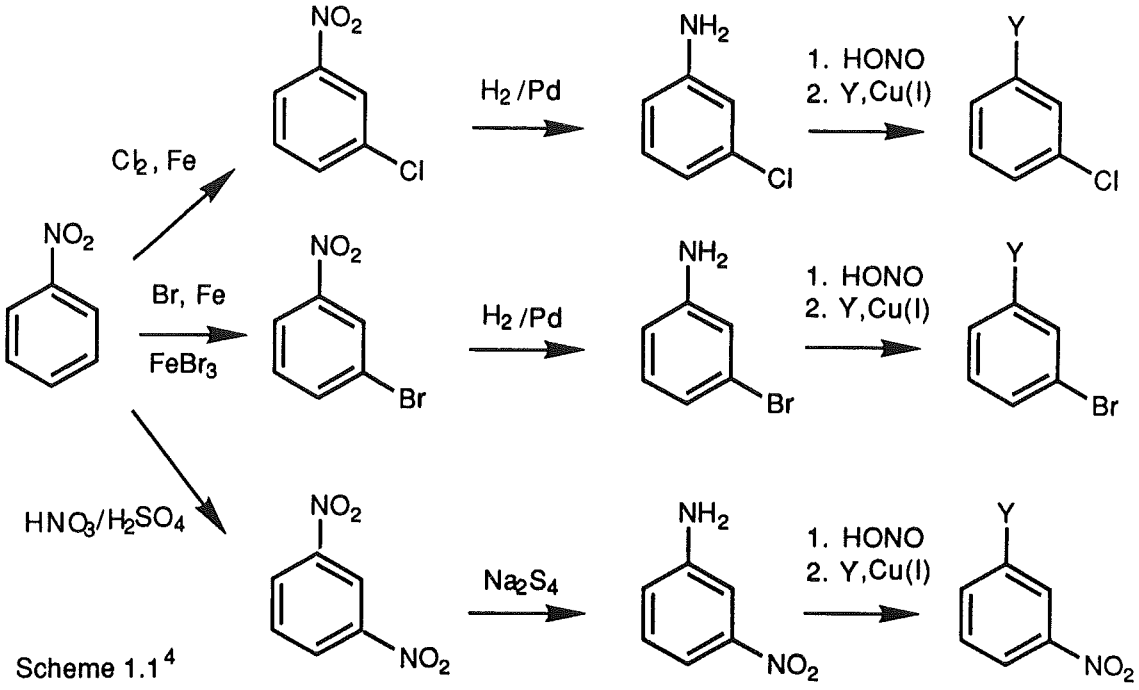
Chapter 1
Introduction.

1 The Importance of Nitration.

Nitration is important for three reasons: First, it is the most general method used in the preparation of aromatic nitro compounds. Second, nitration reactions have played and they continue to play an important role in the development of our understanding of aromatic electrophilic substitution reactions. And third, nitrated aromatic compounds are of interest because they are often mutagenic compounds of great environmental interest.

1.1 Nitration as a Preparative Technique.

The extensive use of aromatic nitro compounds in industry as compounds in their own right (for example, explosives) and as important precursors to other aromatic compounds (for example, amines and azo-dyes) exemplifies the importance of aromatic nitration reactions in industrial chemistry. Aromatic nitration reactions are also used preparatively in research. The nitrated aromatic itself may be required as, for example, a standard compound for chromatography,[1] or the nitrated compound may be required as a precursor to another compound. In particular, nitration followed by reduction to give an aniline is very useful synthetically because when an aniline is treated with sodium nitrite in acid a diazonium salt is formed. Diazonium salts are common precursors to: biphenyls, phenols, nitriles, halo (chloro, bromo, iodo, fluoro), organometallic compounds (Hg, Tl, Sn, Pb, Sb, Bi), azo-compounds and triazines.[2, 3] Because of the *meta* directing nature of the nitro group in electrophilic aromatic substitution, this reduction-diazonium salt pathway is used to prepare *meta* - substituted benzenes,[4] Scheme 1.1.



Scheme 1.1[4]

1.2 Electrophilic Aromatic Substitution.

Electrophilic (ionic) aromatic substitution reactions have been studied extensively and the general features of these reactions are well-understood. The commonly accepted mechanism of these reactions is summarized in Figure 1.1, below. This reaction mechanism is described as the arenium ion mechanism.[2]

Figure 1.1

The nitronium ion and the aromatic compound diffuse together to give an "encounter pair" represented by [ArX.NO_2^+] which is of undefined structure. This encounter pair produces the relatively unstable σ-complex (arenium ion, Wheland intermediate[5]) which generates nitro-compounds by loss of X^+.

In conventional electrophilic aromatic substitution X is a hydrogen atom and the product is formed *via* simple proton loss. When the substrate is a substituted aromatic compound another Wheland intermediate, W_i^x , is possible. Figure 1.2.

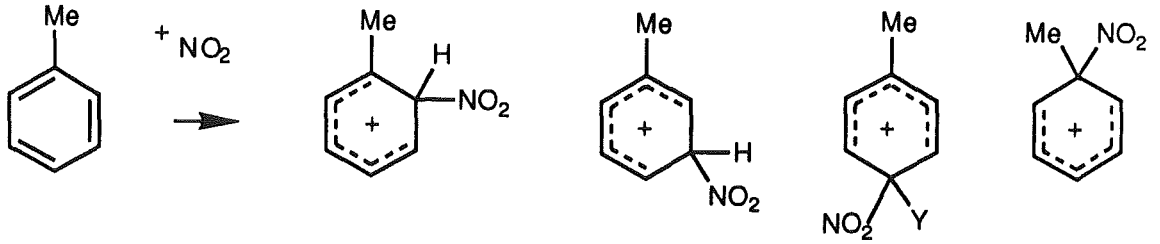
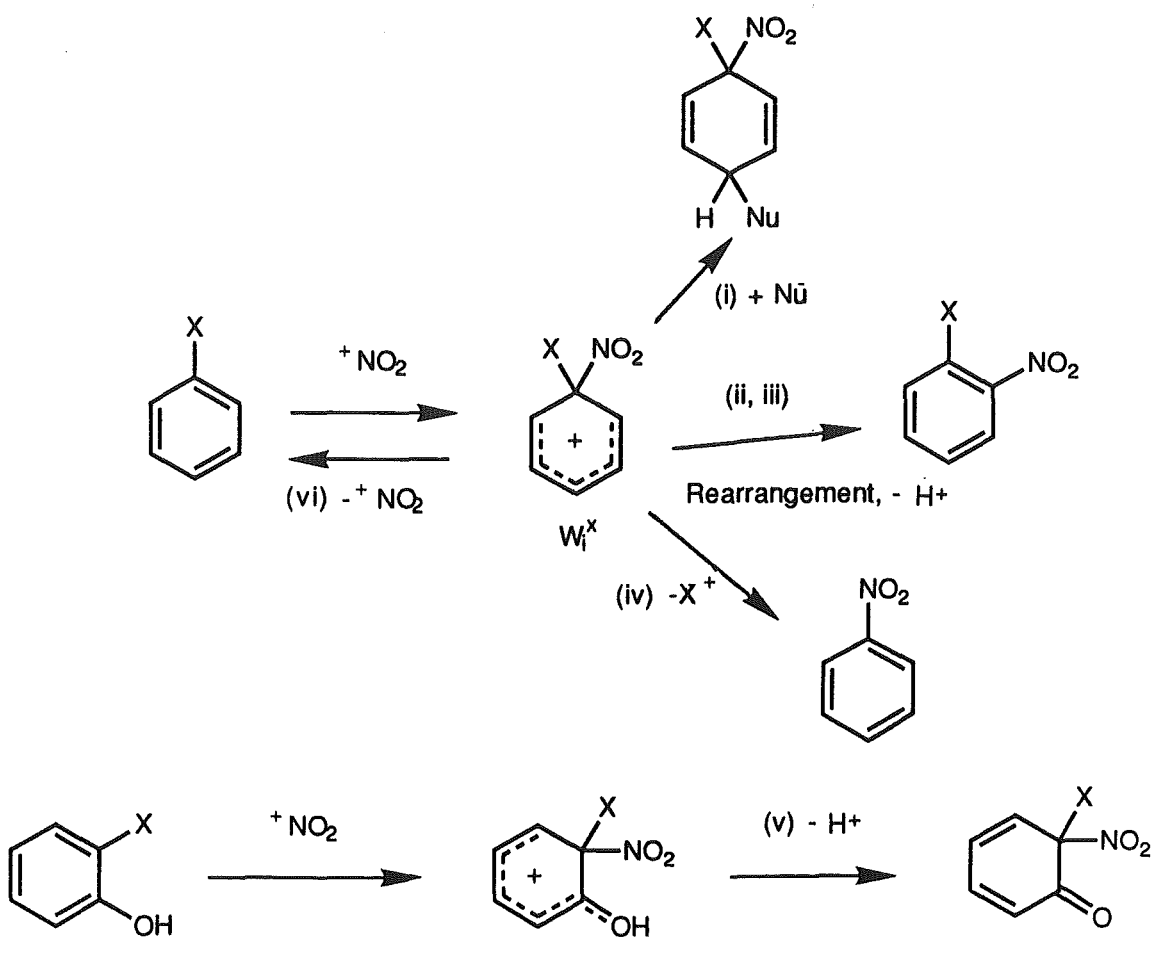


Figure 1.2 W_o W_m Wp W_i^x

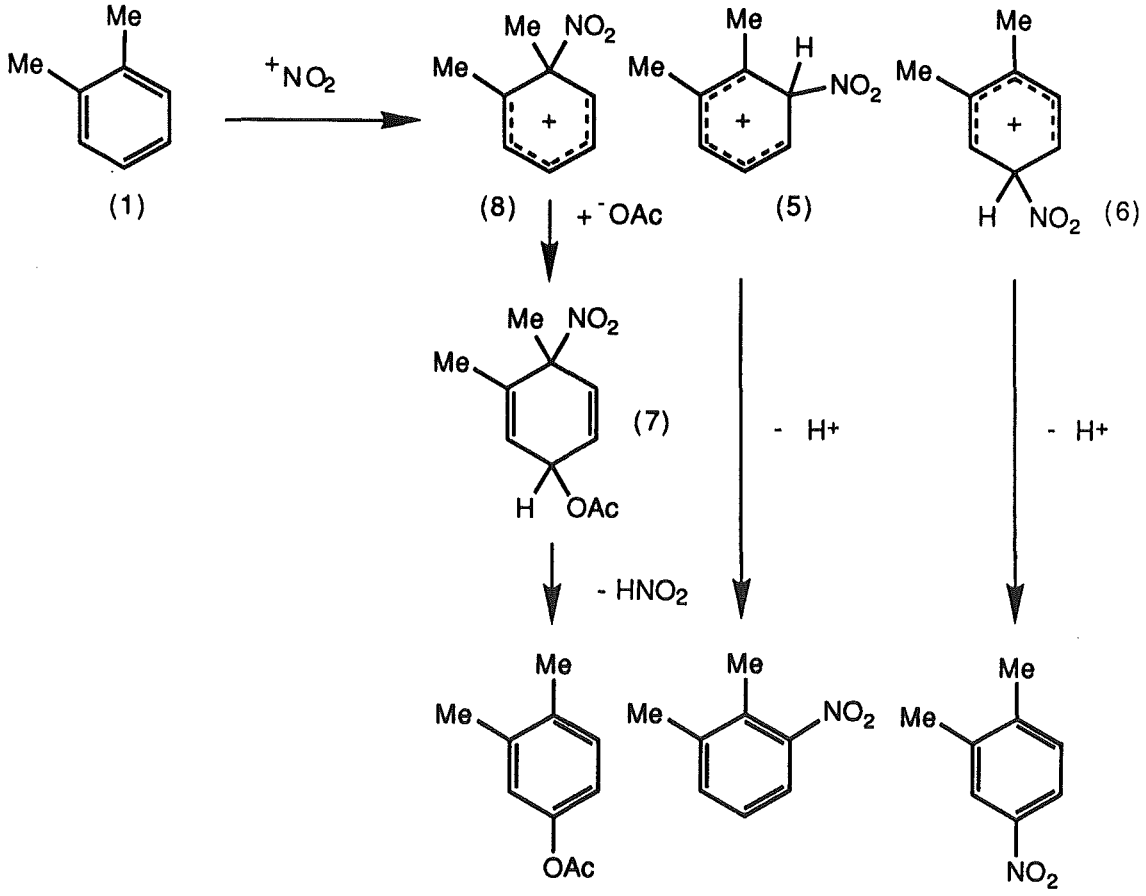
This *ipso*-Wheland intermediate (W_i^x)[6] cannot simply lose a proton to give a nitrated product. Instead, further reaction may occur by so called "unconventional" pathways.[7] These include the reaction pathways outlined in Scheme 1.2, namely: (i) capture of the *ipso* -Wheland intermediate by a nucleophile, (ii) 1,2-migration, followed by proton loss, (iii) similar migration of X, followed by proton loss, (iv) loss of X, *i.e. ipso* - substitution, (v) loss of a proton or a related group from a substituent remote to the *ipso* -position and (vi) return to starting material. Examples of these, with further comment, are given below:



Scheme 1.2

1.2.1 Capture of the Ipso-*Wheland Intermediate by a Nucleophile.*

In one of the earliest studies of *ipso* -substitution, nitration of 1,2-dimethylbenzene (1) in acetic anhydride gave 4-acetoxy-1,2-dimethylbenzene (2) in addition to the nitro compounds, 1,2-dimethyl-3-nitrobenzene (3) and 1,2-dimethyl-4-nitrobenzene (4), Scheme 1.3.



Scheme 1.3 (2) 51% (3) 16% (4) 33%

The nitro compounds (3) and (4) were formed by simple proton loss from the Wheland intermediates (5) and (6). 4-Acetoxy-1,2-dimethylbenzene (2) is the product of elimination of nitrous acid from the intermediate diene (7). This diene (7) was formed by capture of the *ipso*- Wheland intermediate (8) by acetate ion from the solvent.[8,9]

1.2.2 1,2-Migration, Followed by Proton Loss.

The Wheland intermediate formed by *ipso* -nitration is formally capable of rearranging in two ways. In one the rearrangement involves migration of the nitro-substituent and in the other migration of the *ipso* -substituent, X, occurs. Migration of the *ipso* -substituent has been claimed rarely as it cannot be easily distinguished from direct nitration at an adjacent unsubstituted position.[10, 11] Migration of the nitro-substituent was first proposed by Myhre to explain the acidity dependence of the ratio of 1,2-dimethyl-3-nitrobenzene (3) to 1,2-dimethyl-4-nitrobenzene (4) when 1,2-dimethylbenzene (1) is nitrated in sulphuric acid.[12, 13] See Figure 1.2 and Scheme 1.4, below.

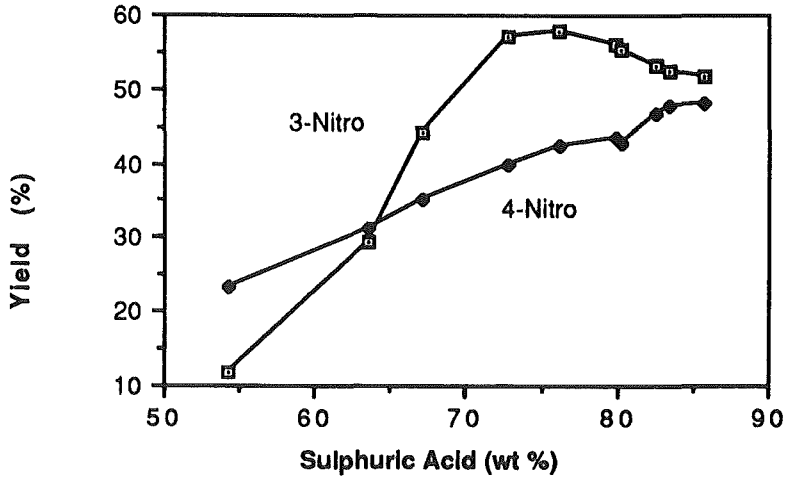
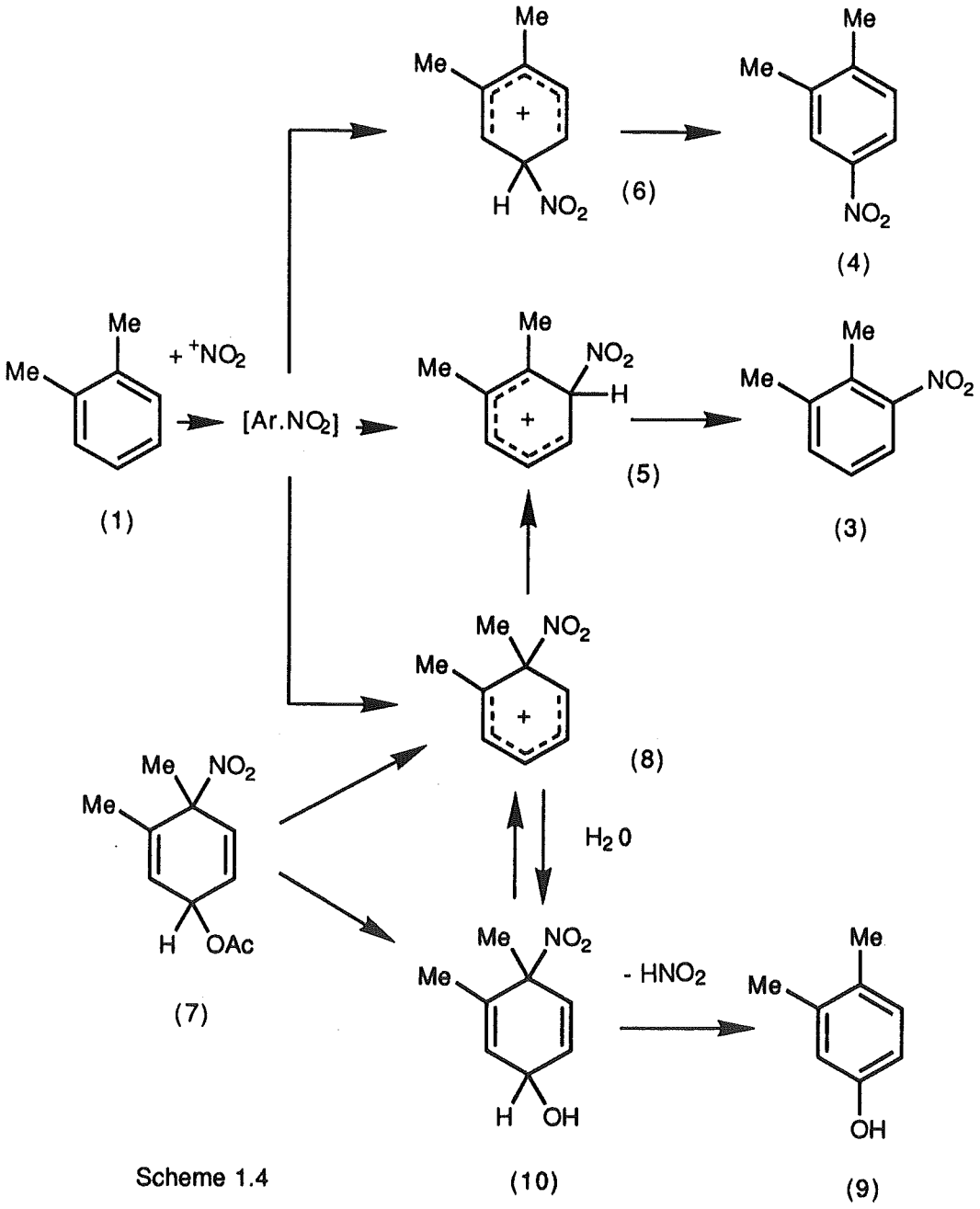


Figure 1.2 Nitration of 1,2-Dimethylbenzene.

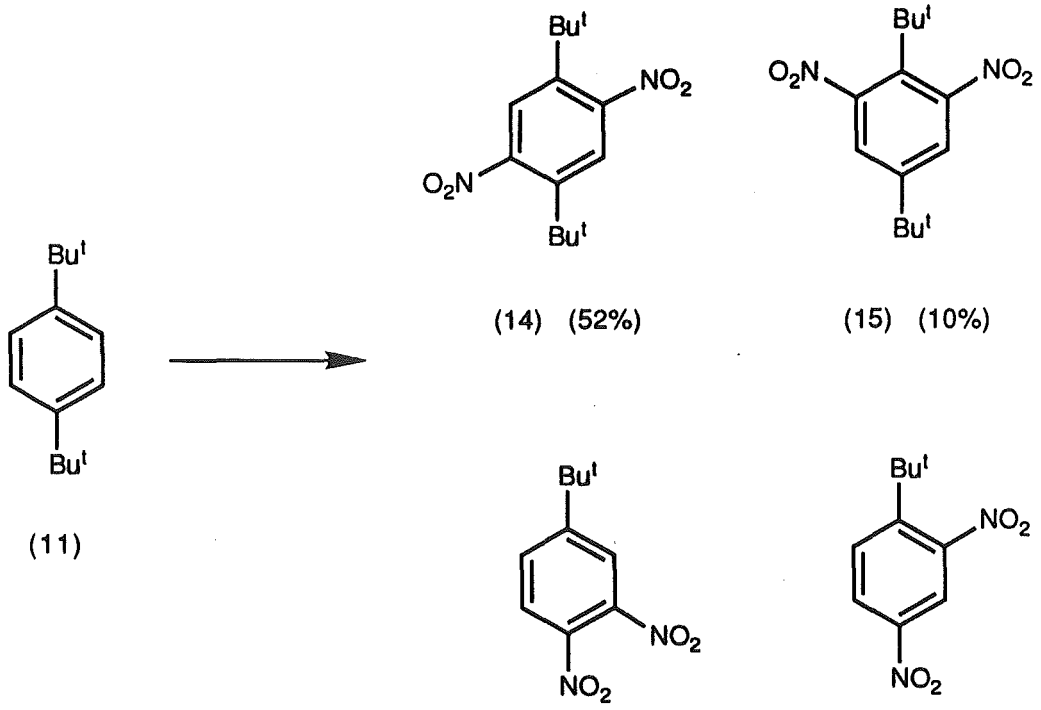
Myhre proposed that the Wheland intermediate (8) is captured by water at low acidities to give 3,4-dimethylphenol (9) (63%) but that as the acidity of the medium was increased 1,2-nitro migration became more important and the major products became the nitroaromatics (3) and (4) (combined total yield 100%). Solvolysis of the high melting isomer of 1-acetoxy-3,4-dimethyl-4-nitro-2,5-cyclohexadiene (7) gave 1,2-dimethyl-3-nitrobenzene (3) in addition to 3,4-dimethylphenol (9). The important observation was that no 1,2-dimethyl-4-nitrobenzene (4) was found. Return of the Wheland intermediate (8) to the encounter pair does not, in this case, compete with either nitro migration to produce 1,2-dimethyl-3-nitrobenzene (3) or with capture by water to give 3,4-dimethylphenol (9).[14]


Me
Me
+ +NO2
[Ar.NO2]
(1)
Me
Me
H NO2
(6)
Me
Me
NO2
(4)
Me
Me
NO2
H
(5)
Me
Me
NO2
(3)
Me NO2
Me
(8)
H2 0
Me NO2
Me
H OAc
(7)
Me NO2
Me
H OH
(10)
- HNO2
Me
Me
OH
(9)

Scheme 1.4

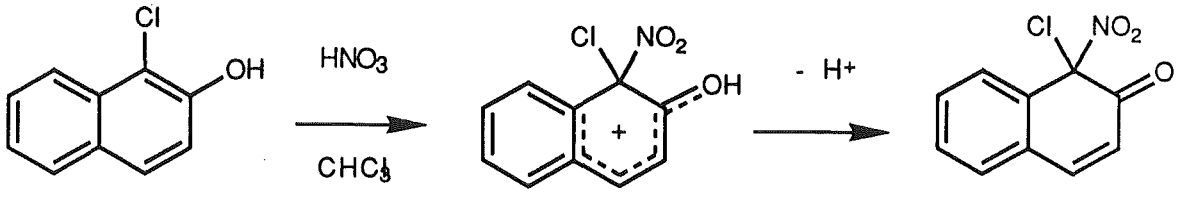
1.2.3. Ipso-*Substitution.*

Ipso -substitution is the longest-known result of *ipso* -attack. It occurs when the *ipso* group (other than the nitro) is acyl, alkyl, aryazo, aryloxy, carboxyl, halogen, methoxyl, phosphonyl, silyl or sulphonyl. This reaction type has been much-studied, but none the less in some cases the mode of removal of the non-nitro *ipso* group remains a matter of debate.[10] For example, nitration of 1,4-di-*t* -butylbenzene (11) gave two mono-*t* -butyl compounds (12) (9%) and (13) (11%) in addition to the "conventional" products: (14) (52%) and (15) (10%), Scheme 1.5.[15] Loss of the stable *t* -butyl cation from the *ipso* -Wheland intermediate was proposed to rationalize the formation of the "unconventional" products (12) and (13).



Scheme 1.5

In a further example, Perrin[16] showed that the relative leaving abilities of the electrophiles Cl^+, NO_2^+ and Br^+ increased in the order: $Cl^+ < NO_2^+ < Br^+$. Reaction of 1-chloro-2-naphthol (16) with nitric acid in chloroform gave the 1-chloro-1-nitro-2-keto compound (17). Scheme 1.6.

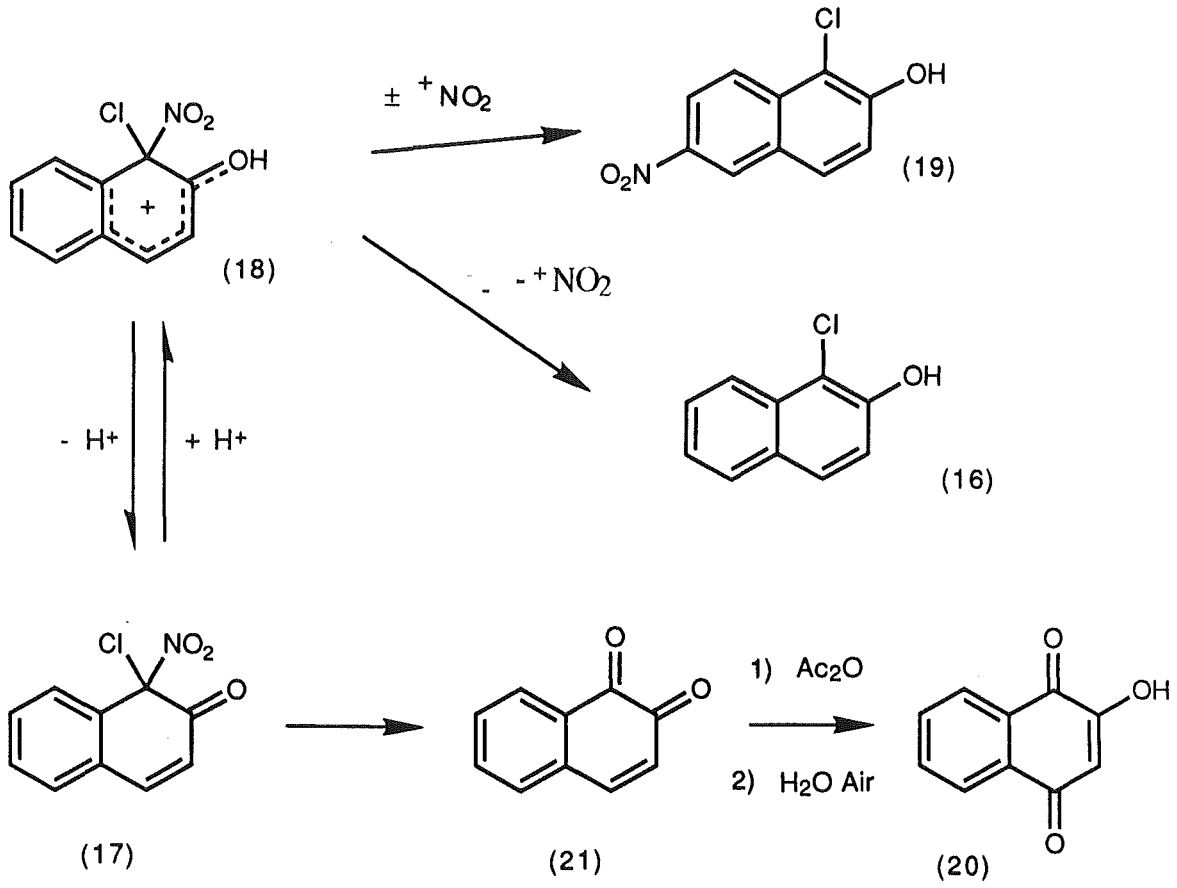


(16) (18) (17)

Scheme 1.6

This compound was thought to be formed *via* proton loss from the *ipso* -Wheland intermediate (18). On treatment under acidic conditions, with hydrogen chloride and urea in a mixture of acetic acid and acetic anhydride, compound (17) reacted further *via* the *ipso* -Wheland intermediate (18) to give 1-chloro-6-nitro-2-naphthol (19) and 1-chloro-2-naphthol (16); a further compound, 2-hydroxy-1,4-naphthoquinone (20) was also isolated. This latter compound (20) was formed from the non-protonated 1-chloro-1-nitro-2-keto compound (17). The major product, 1-chloro-6-nitro-2-naphthol (19), was formed by an intramolecular rearrangement of the *ipso* -nitro substituent. That the nitro-substituent had migrated rather than the chloro-substituent showed that the relative leaving ability of the two substituents is $Cl^+ < NO_2^+$. The minor product, 1-chloro-2-naphthol (16), was formed by the loss of the nitro-substituent from the *ipso* -Wheland intermediate (18), Scheme 1.7.

In contrast, nitration of the bromo analogue of (17) gave only 1-nitro-2-naphthol. That the bromo substituent was lost, rather than the nitro substituent, showed that the relative leaving ability of the two substituents is $NO_2^+ < Br^+$.

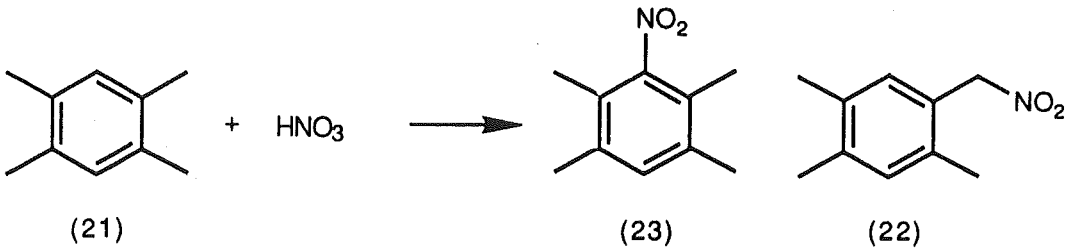


Scheme 1.7

1.2.4 Loss of a Proton or a Related Group from a Substituent Remote From the Ipso *-Position.*

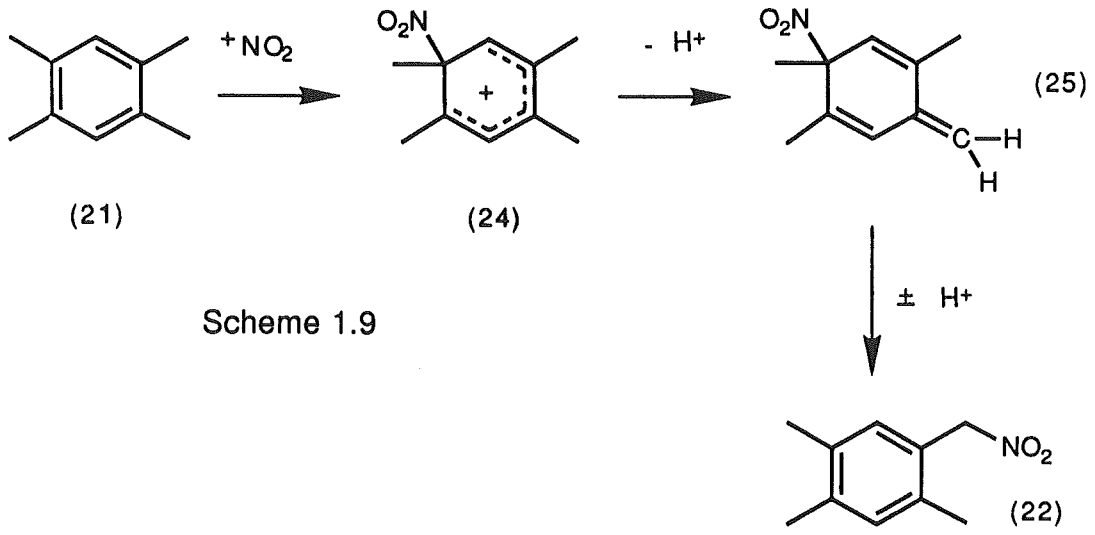
In this thesis two examples of the loss of a proton, or a related group, from a substituent remote from the *ipso* -position are important. The first, the formation of a nitrocyclohexadienone from the reaction of a phenol with nitric acid, will be discussed in the introduction to Chapter 2 [This pathway is shown in Scheme 1.2, pathway (v)].

The second type of reaction leads to overall side-chain nitration, and many examples of this reaction are known.[10] For example, nitration of 1,2,4,5-tetra-methylbenzene (21) in nitric acid in acetic anhydride gave the "unconventional" product, 1-nitromethyl-2,4,5-trimethylbenzene (22) in addition to 1-nitro-2,3,5,6-tetramethyl-benzene (23).[17] Scheme 1.8.



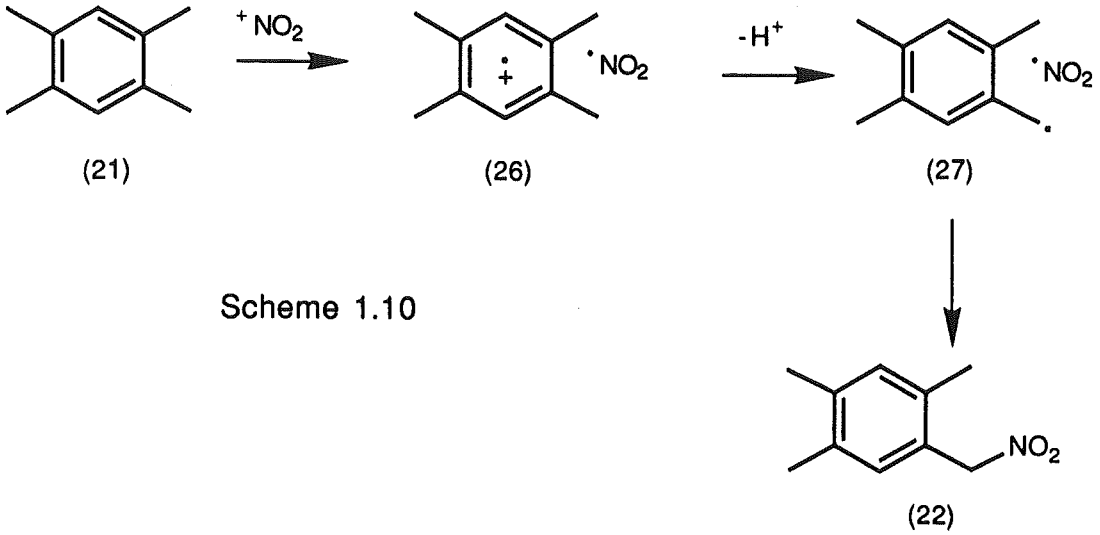
Scheme 1.8

Two distinct mechanisms have been proposed to account for side-chain nitration under ionic reaction conditions:[18] The first mechanism involves electrophilic addition to give the Wheland intermediate (24) followed by proton loss to give a methylenecyclohexadiene (25). This is followed by a sigmatropic rearrangement to give the product (22). Scheme 1.9. The best evidence for this mechanism is the observation (^{1}H n.m.r.) of the intermediate triene (25) at low temperature and its subsequent rearrangement to give product (22).[19]



Scheme 1.9

The second mechanism, involves electron transfer to give an aromatic cation radical (26), followed by deprotonation to give the radical species (27). Subsequent coupling between nitrogen dioxide and the radical (27) would then give the product (22). Scheme 1.10. Evidence for this mechanism consists of the isolation of side-chain nitrated compounds when the aromatic cation radical is prepared *via* some other route.[18]



(21) (26) (27)

(22)

Scheme 1.10

1.2.5 Orientation and Reactivity in Substituted Benzene Rings.

When an electrophilic substitution reaction is carried out on a monosubstituted benzene, the new group will be directed by electronic effects to (primarily) the *meta,* or *ortho* and *para* positions. *Meta* directing substituents are deactivating, *i.e.* they slow the reaction relative to benzene; *ortho/para* directing substituents are mostly activating. Only small amounts of material consequent of *ipso-* substitution is observed. When the substitution reaction is on a benzene ring with more than one substituent the expected product(s) can be predicted as a result of a combination of the directing effects of the substituents.[2] Favourably placed groups can greatly increase the proportion of products formed as the result of *ipso* -attack. This can be seen in Figure 1.3 where the positional selectivity of a series of methyl-benzenes is shown.[10] The methyl group is activating and *ortho/para* directing in electrophilic aromatic substution.

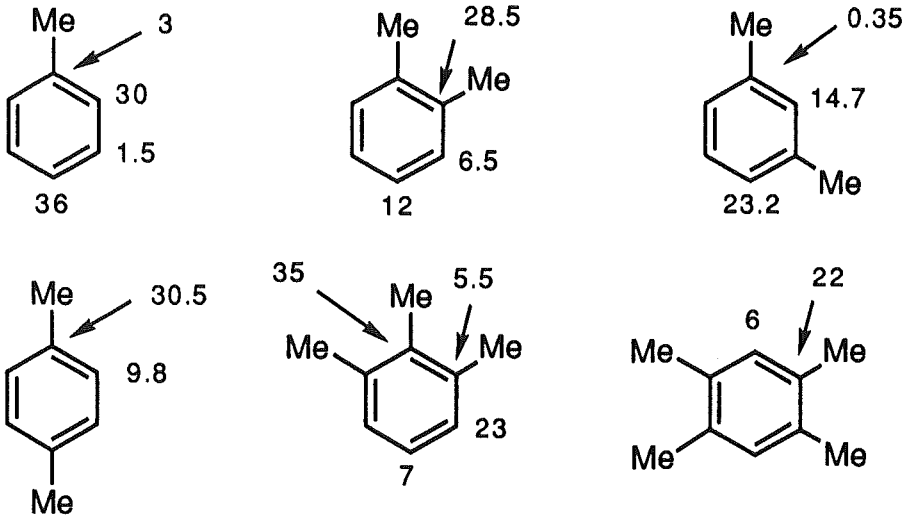


Figure 1.3

1.3 Nitration with Nitrogen Dioxide and Dinitrogen Tetroxide.

Although the literature of nitration reactions is predominantly concerned with nitration *via* electrophilic aromatic substitution, where the nitrating species is the nitronium ion (NO_2^+), there are also significant references[20, 21, 22] to free-radical nitration by the lower oxides of nitrogen, N(III) and N(IV). Of particular relevance to this thesis are references to nitration reactions where the unpaired-electron species nitrogen dioxide ($^{\bullet}NO_2$) is the nitrating agent. This topic has been reviewed by: Riebsomer,[23] 1945; Gray and Yoffe,[24] 1955; Topchiev,[25] 1959; Titov,[20] 1963; and Rees and Williams,[26] 1969. There is no recent review although a great deal of research has been done.

1.3.1 Nitrogen Dioxide As a Reagent.

Nitrogen dioxide exists in a strongly temperature dependent equilibrium with its dimeric form dinitrogen tetroxide. Dinitrogen tetroxide freezes at -12.2°,[27] and below this temperature it exists as a white solid. X-ray analysis of the solid reveals a bond length of 1.17Å for the N-N distance, and an O-N-O angle of 126°. At room temperature dinitrogen tetroxide exists as a mixture of dimeric N_2O_4 in equilibrium with the monomer, nitrogen dioxide radical ($^{\bullet}NO_2$), formed by homolytic dissociation of the N-N bond of dinitrogen tetroxide. This equilibrium is strongly temperature dependent. In the liquid state between -11.2° and 21.2° the system may be considered a dilute solution of $^{\bullet}NO_2$ in N_2O_4, the dimer

being the predominant species. At 100° the vapour consists mainly of monomeric nitrogen dioxide radicals (*c.* 90%).

$$N_2O_4 \rightleftharpoons 2\ {}^{\bullet}NO_2$$

Colourless diamagnetic — Brown paramagnetic

In solution, the position of the N_2O_4/NO_2 equilibrium is shifted to the left (favouring N_2O_4) due to a drastic lowering of the entropy of dissociation with respect to the gas phase. There is little change in the enthalpy of dissociation.[28, 29] In the gas phase the equilibrium constant (K_c^{298}) is 1.51×10^{-1} mol l^{-1}, this value is reduced to 1.77×10^{-4} mol l^{-1} in non-coordinating solvents such as cyclohexane and carbon tetrachloride. In coordinating solvents such as acetonitrile or acetic anhydride an additional decrease in K_c is observed [K_c^{298} (CH_3CN) 0.3×10^{-4} mol l^{-1}] due to an association of the N_2O_4 molecule with the solvent. This association is reflected in an increase in the enthalpy of dissociation of N_2O_4.

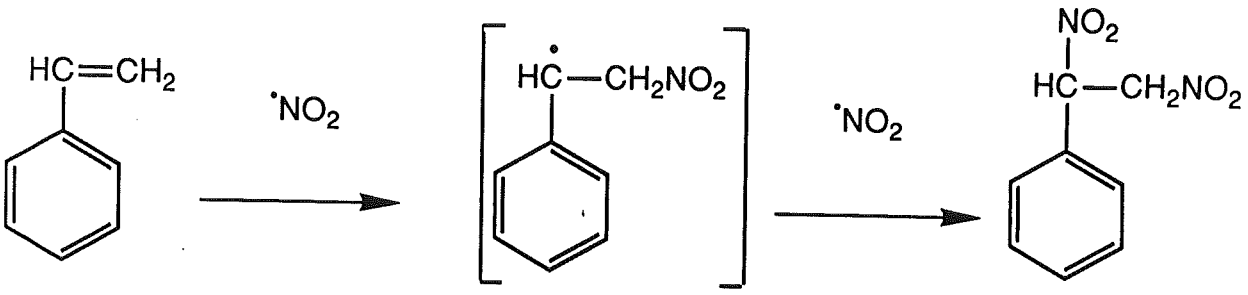
The monomeric unpaired electron species ${}^{\bullet}NO_2$ has been the subject of extensive e.s.r. spectroscopic investigations to determine the location of the unpaired electron spin density. This is distributed so that approximately 50% is located on the nitrogen atom, with the remaining 50% being shared evenly between the two oxygen atoms.[30, 31, 32] Because of the differing electronegativities of nitrogen and oxygen, nitrogen dioxide also has an electric dipole moment (0.316 D); the nitrogen centre of the radical is electrophilic in character and the two oxygen centres are nucleophilic in character.[27] This dual nature of the nitrogen dioxide radical is well described by the four resonance contributors shown below, Figure 1.4.

$$\left[\dot{O}{-}N{=}O \longleftrightarrow O^{-}{-}N^{+\bullet}{=}O \longleftrightarrow O{=}N^{\bullet+}{-}O^{-} \longleftrightarrow O{=}N{-}\dot{O} \right]$$

Figure 1.4

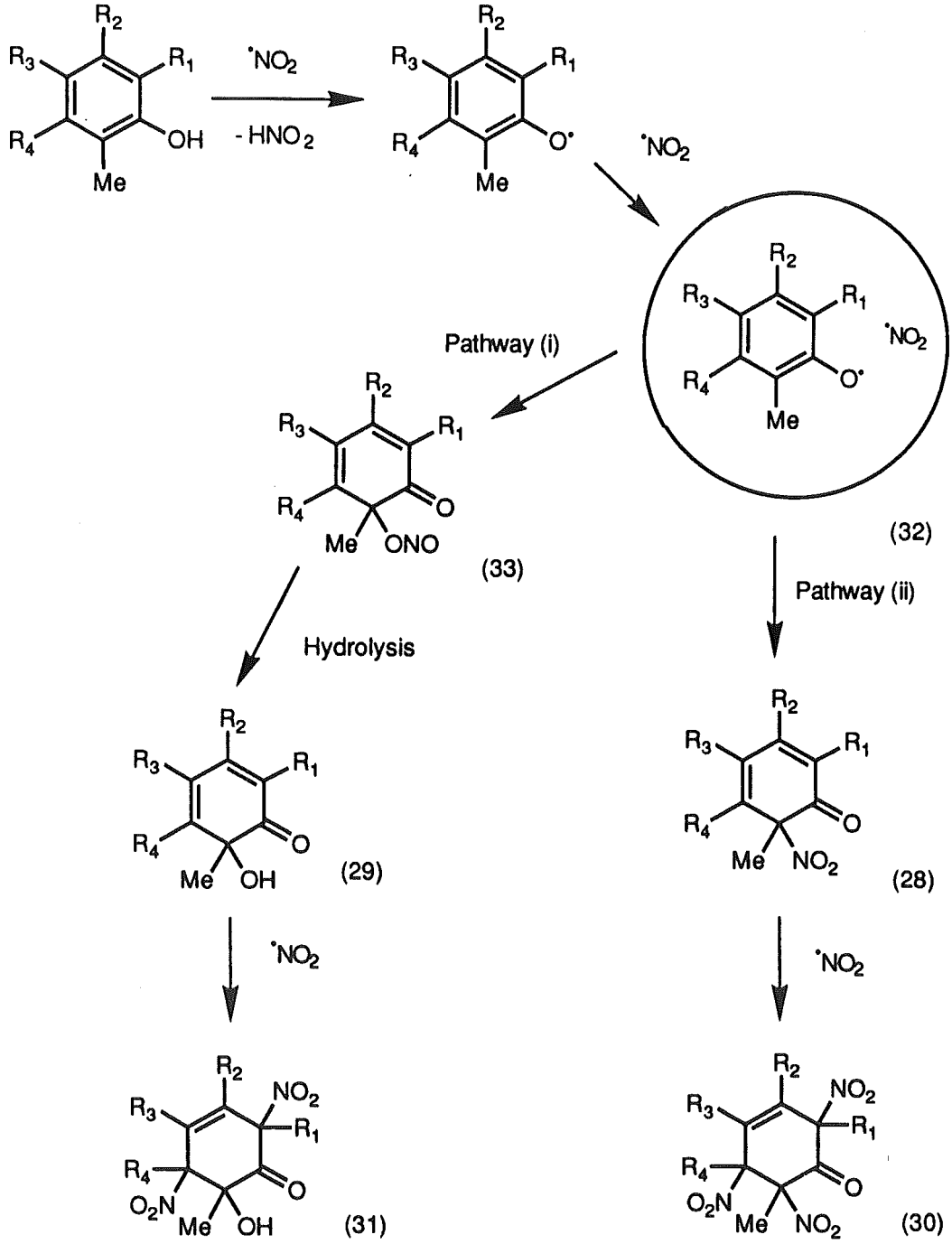
1.3.2 Reactions of Nitrogen Dioxide.

Addition of nitrogen dioxide to unsaturated organic systems, such as carbon-carbon double bonds and aromatic nuclei, has been shown to involve free-radical intermediates. For example, the reaction of styrene with nitrogen dioxide has been shown to proceed *via* free-radical intermediates,[33] Scheme 1.11.



Scheme 1.11

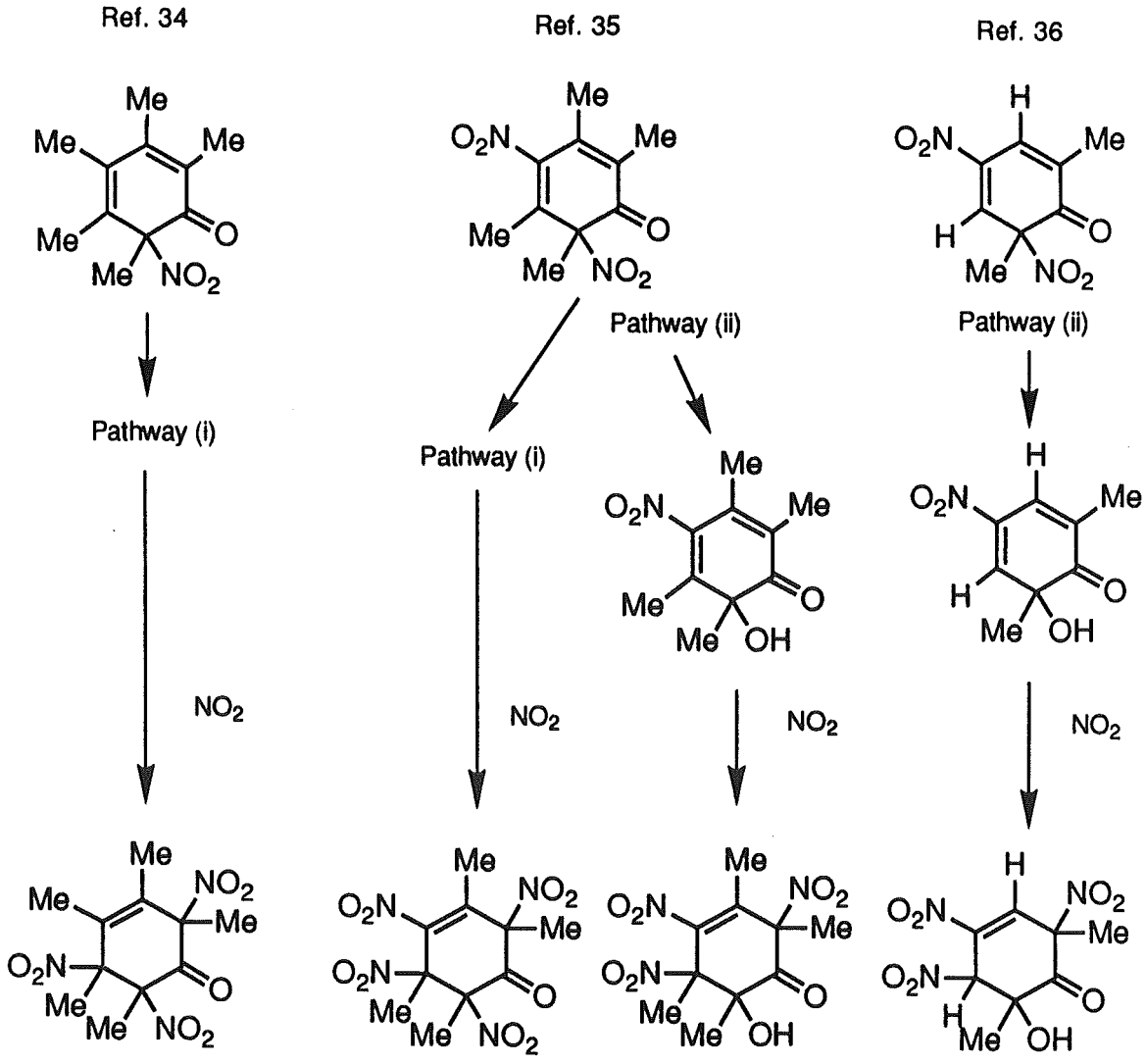
Evidence that the charge separation on nitrogen dioxide influences the course of reaction is found when the products of the reaction of nitrogen dioxide with pentamethylphenol[34], 2,3,5,6-tetramethyl-4-nitrophenol[35], and 2,6-dimethyl-4-nitrophenol[36] are compared.[37] Phenols react with nitrogen dioxide to give polynitrocyclohexenones *via* 6-nitrocyclohex-2,4-dienones (28) and 6-hydroxycyclohex-2,4-dienones (29).



Scheme 1.12

These 6-nitrocyclohex-2,4-dienones (28) and 6-hydroxycyclohex-2,4-dienones (29) then react quantitatively with further nitrogen dioxide to give 6-nitrocyclohex-3-enones (30) and 6-hydroxycyclohex-3-enones (31), Scheme 1.12. The important point here is that the partition from the solvated radical pair (32) to the 6-nitrocyclohex-2,4-dienones (28) and to the 6-nitritocyclohex-2,4-dienones (33) is critically dependent on the electronic nature of R_1, R_2, R_3, and R_4. Substrates with electron-withdrawing substituents, e. g. the nitro group, favour attack by nitrogen dioxide at the electrophilic nitrogen centre giving 6-nitrocyclohex-2,4-

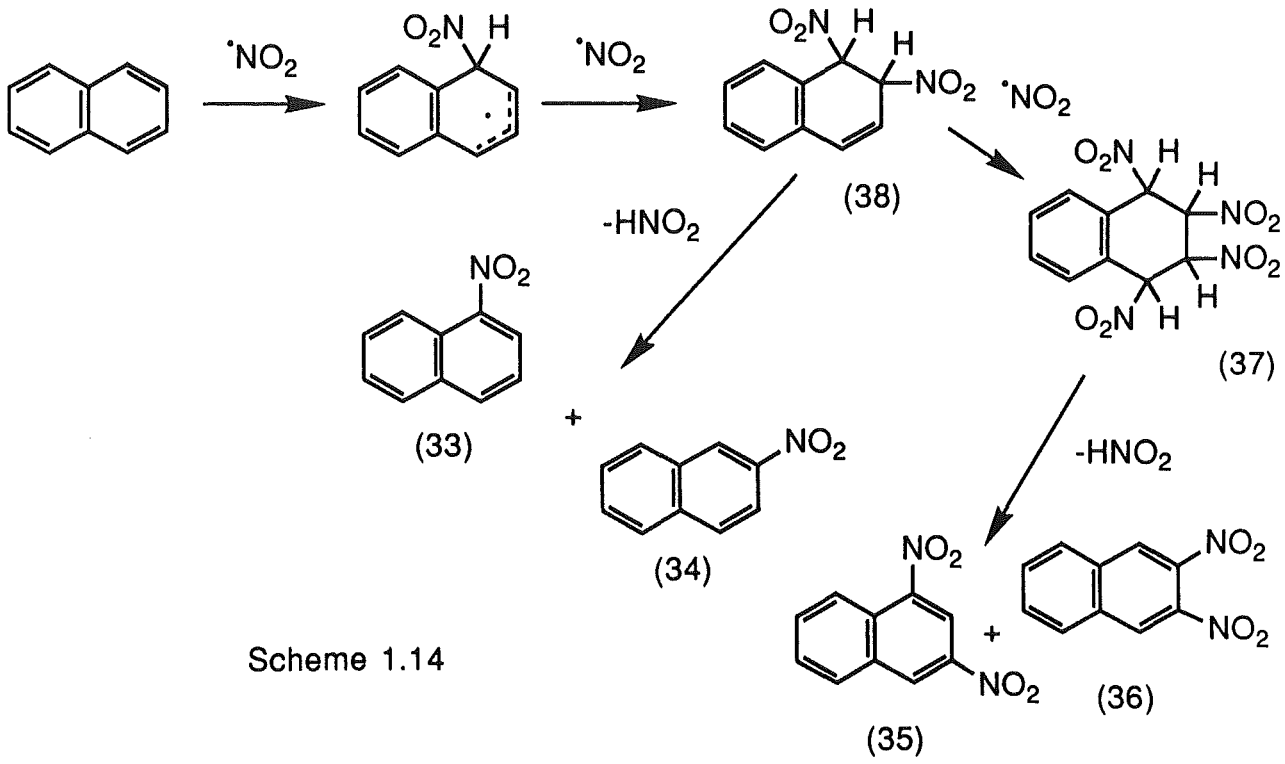
dienones (28) and subsequently 6-nitrocyclohex-3-enones (30). Whereas substrates with electron releasing substituents, e. g. the methyl group, favour attack by nitrogen dioxide at the nucleophilic oxygen centres giving 6-nitritocyclohex-2,4-dienones (33) and subsequently 6-hydroxycyclohex-3-enones (31). Scheme 1.13 gives examples of this substituent effect. That nitrogen dioxide behaves in this way is consistent with the dual nature of nitrogen dioxide described above.



Scheme 1.13

Reaction of nitrogen dioxide with naphthalene in carbon tetrachloride is also thought to proceed by a radical mechanism.[38] Two observations, inconsistent with an electrophilic mechanism, point to this. First, the ratio of 1-nitronaphthalene (33) to 2-nitronaphthalene (34) is low (about 4) compared to that observed under electrophilic conditions (about 10). Second,

small amounts of 1,3-dinitronaphthalene (35) and 2,3-dinitronaphthalene (36) are isolated. Because of the deactivating *meta* -directing nature of the nitro-group in aromatic electrophilic substitution these products were regarded as unprecedented in the literature of nitronium ion reaction with naphthalene and its derivatives. The expected products of resubmission of 1-nitronaphthalene (33) under electrophilic conditions are 1,6-dinitro-naphthalene and 1,7-dinitro-naphthalene and the expected products of resubmission of] 2-nitronaphthalene (34) under electrophilic conditions are 1,8-dinitronaphthalene and 1,5-dinitronaphthalene.[39] The dinitrated compounds (35) and (36) are formed by an addition-elimination mechanism with loss of nitrous acid from the tetranitro intermediate (37) giving the dinitrated compounds (35) and (36) and loss of nitrous acid from the dinitro intermediate (38) giving the mononitrated products (33) and (34), Scheme 1.14. Intermediates (37) and (38) could not be isolated. However, compounds analogous to (38) have recently been isolated from the reaction of anthracene with nitrogen dioxide in carbon tetrachloride.[38] The isolation of *cis* and *trans* 9,10-dinitro-9,10-dihydroanthracene provide indirect proof for the proposed intermediates (37) and (38). Multiple addition intermediates of varying stability appear to be a common feature in the radical nitration of polyaromatic hydrocarbons because of the difficulty of removing the very unstable hydrogen atom, •H. This is in sharp contrast with electrophilic nitration where the σ-complexes normally lose their acidic proton rapidly by transfer to solvent. That the dinitrated compounds (35) and (36) are formed in this way rather than by subsequent reaction of the mononitrated compounds (33) and (34) was shown when it was found that the dinitrated compounds (35) and (36) are formed early in the reaction rather than later.[38]



Scheme 1.14

Under comparable conditions the reaction of fluoranthene with nitrogen dioxide is also thought to proceed by a free radical mechanism.[40] The distinctive features of the reaction with nitrogen dioxide in carbon tetrachloride compared to the reaction with nitric acid in acetic anhydride (*i.e.* electrophilic conditions) are much the same as in the naphthalene case, above. Formation of much greater yields of 2-nitrofluoranthene and much lower yields of 8-nitrofluoranthene, the production of modest yields of dinitrofluoranthenes even at low conversions and disubstitution giving dinitrofluoranthenes always occurring in the same ring point to a free radical rather than an electrophilic nitration mechanism.

1.4 Nitroaromatics in the Environment.

Nitrated polycyclic aromatic compounds (nitro-PAHs) are ubiquitous anthropogenic compounds which have been isolated from ambient particulate organic matter, diesel and gasoline exhaust particulates, soot, cigarette smoke, and coal fly ash.[41-48] This is important because many nitro-PAHs are strong direct mutagens and some have been found to be carcinogenic in laboratory animals.[49-51] The isolation of nitro-PAHs in environmental samples is thought to be the result of their formation by three possible routes. The nitro-PAHs may be formed (i) during the condensation reactions leading to the polycyclic aromatic

compounds, (ii) by chemical reaction between parent PAHs and NO_x in the atmosphere, (iii) as the result of chemical reaction between the parent PAHs and NO_x on the filters used to collect the organic particulate material. Examples of all three pathways are found in the literature.[42, 43, 45, 47, 52-56]

In an early study in this area Pitts *et. al.* deposited benzo[*a*]pyrene (BP), and perylene onto the surface of glass fibre filters and exposed each to pollutant gases under simulated atmospheric conditions (Benzo[*a*]pyrene is a known direct mutagen and perylene is not).[57] In the event the authors isolated 1- and 3-, and 6-nitrobenzo[*a*]pyrene and 3-nitroperylene. These nitration products were then subjected to Ames tests for mutagenic activity with *Salmonella typhimurium* strains. These tests were carried out with, and without, addition of a mammalian metabolic activation system. The nitrated PAHs were found to be direct mutagens and in the case of the nitro-BP isomers the mutagenicity was significantly greater than that of the parent PAH. The dose response curves are shown in Fig. 1.5.

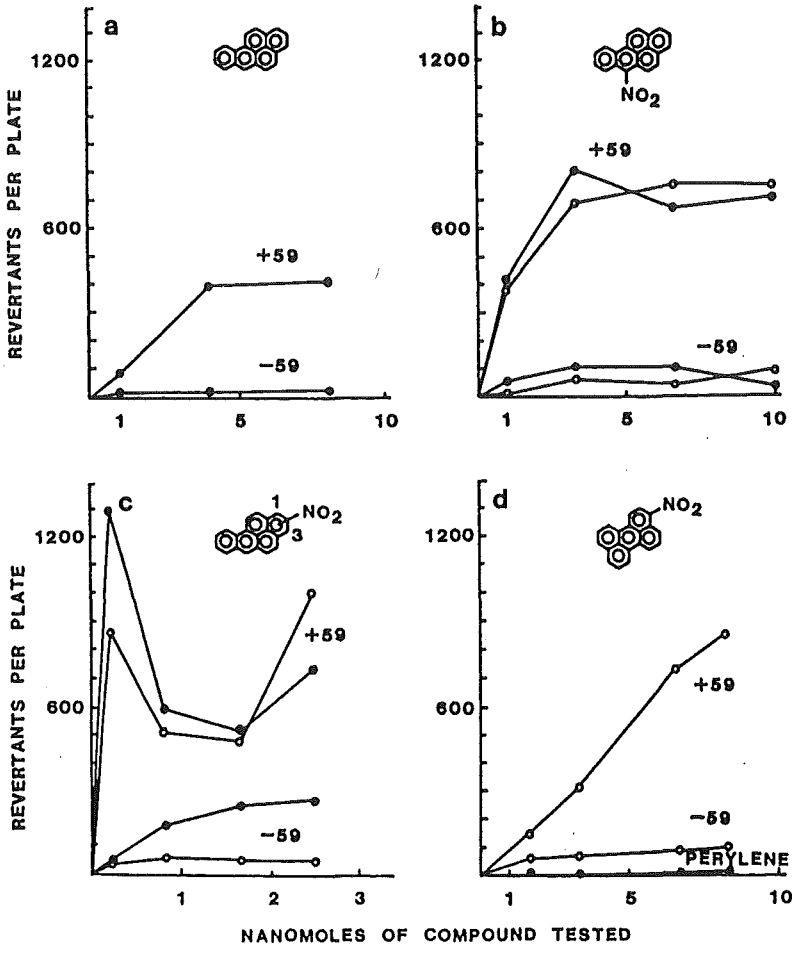


Figure 1.5

In another example, Hanson *et. al.* extracted fly ash from the combustion of coal and then tested the extracts for mutagenicity with Ames tests to obtain mutagenic and non-mutagenic fractions.[58] Two samples were extracted with dichloromethane. Sample 1 was mutagenic and sample 2 was non-mutagenic. The dichloromethane extracts were analysed by gas chromatography/mass spectroscopy and by mass spectroscopy/mass spectroscopy. The mutagenic fractions contained much higher levels of dinitrated PAHs than the non-mutagenic fractions. In another experiment the two samples were treated with dinitrogen tetroxide and the mutagenicity was tested. Nitration greatly increased the direct mutagenicity and analysis showed increased levels of both nitro- and dinitro- PAHs. The results of the mutagenicity tests are shown in Table 1.1 and the analytical results are shown in Table 1.2. In addition to the isolation of nitro- and dinitro- PAHs from the coal fly ash samples Hanson *et. al.*[58] showed that the nitroaromatic compounds contributed a significant portion of the direct-acting mutagenicity in the *Salmonella* mutagenicity assay.

Table 1.1. Mutagenicity of Two Bag Filter Ash Samples from Fluidized Bed Combustion of Texas Lignite Coal.

	Revertants per microgram of extract or compound (correlation coefficient)		
Material	TA98	TA98+S9	TA98/1,8-DN
Sample 1	28(1.00)	31(0.990)	4(0.993)
Sample 2*	<0.1(0.976)	0.2(0.997)	<0.1(0.434)
Sample 1+N_2O_4	800	41(1.00)	240(0.894)
Sample 2+N_2O_4	320(0.948)	160(0.900)	120(0.939)
1-Nitropyrene	740(0.995)	770(0.975)	740(0.984)
1,8-Dinitropyrene	720000(0.991)	28000(0.995)	25000(0.982)

*The response for sample 2 was at background level.

Table 1.2 Comparison of Lignite Bag Filter Ash Sample for Relative Distribution of PAHs and Mononitro and Dinitro PAHs.

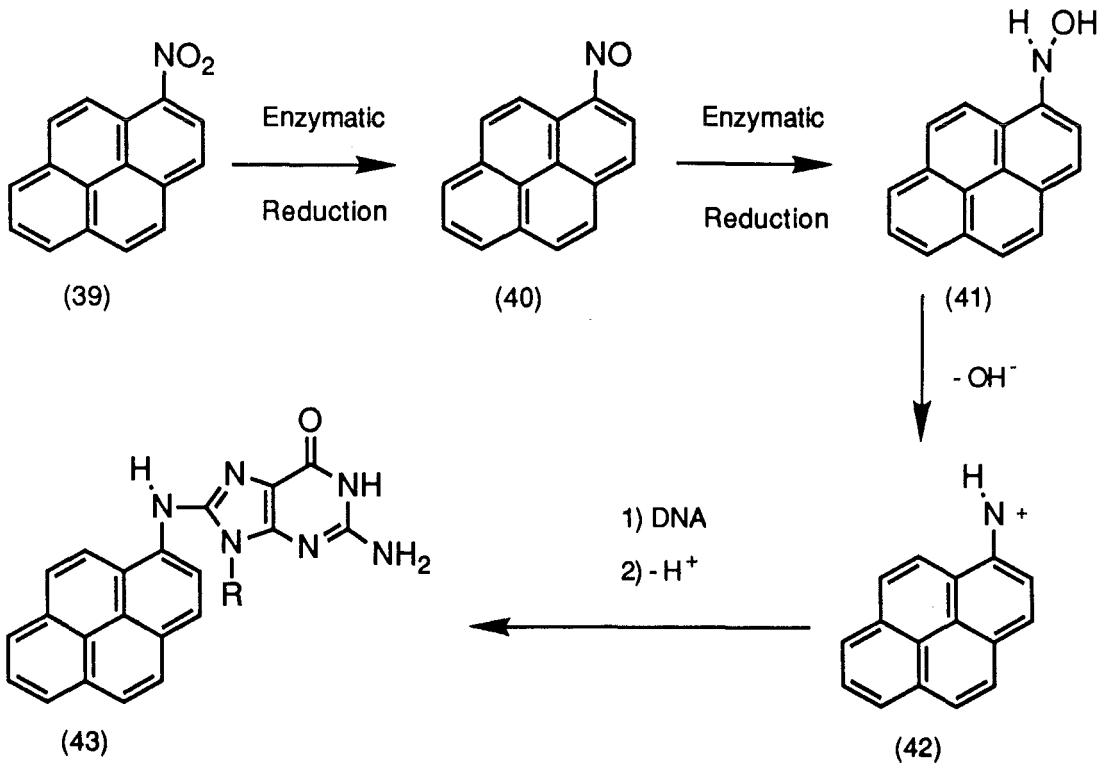
		GC-MS analysis relative intensity*		MS-MS analysis, ion intensity ($x10^{-2}$)** Mononitro isomer.		Dinitro isomer	
		Sample	Sample	Sample	Sample	Sample	Sample
PAH	MW	1	2	1	2	1	2
Naphthalene	128	15	26	9	72	73	63
Methylnaphthalenes	142	1.8	25	3	40	16	13
Biphenyl	154	21	128	5	50	188	16
Phenanthrene	178	100	100	63	173	97	4
Methylphenanthrenes	192	7.7	12	4	28	14	10
Fluoranthene/pyrene	202	128	4.9	50	16	5	ND
Phenylnaphthalenes	204	6.8	31	4	12	18	3

*Summed ion intensities from GC/MS analysis normalized to 100 for phenanthrene.

**40 μg samples. ND: not detected.

1.5 In Vivo *Chemical Transformations Leading to Mutagenic Activity.*

For a chemical to be a mutagen, it or a derivative of it must disrupt the genetic information on DNA. Often this involves formation of an electrophilic species that can then bind to nucleophilic sites on the DNA. Nitroaromatic compounds (39) have been shown to be reduced in *Salmonella typhimurium via* the nitroso-aromatic (40) to give arylhydroxylamines (41). The ultimate mutagen is thought to be an arylnitrenium ion (42). This electrophilic ion then attacks the C8 sites of guanine residues on DNA to give covalent DNA-amino-PAH adducts (43), see Scheme 1.15.[59, 60, 61]



Scheme 1.15

Four structural features are known to correlate with high mutagenicity of nitro-PAHs.[60, 61, 62] These are:

(i) the physical dimensions of the aromatic rings, where the optimal size for mutagenicity is three rings (fluoranthene).

(ii) the isomeric position of the nitro group, nitroaromatics with a nitro group oriented along the long axis of symmetry of the molecule are more potent mutagens than those with the nitro group oriented along the short axis.

These first two factors relate to the ability of the arylnitrenium ion to effectively (physically) intercalate with the bacterial DNA.

(iii) the conformation of the nitro group with respect to the plane of the aromatic ring. Isomeric nitro-PAHs that are sterically crowded at the substituted position, forcing the nitro-group out of plane to the aromatic ring, are more difficult to reduce than isomers with the nitro group in plane and they are therefore less mutagenic.

(iv) the ability of the aromatic ring to resonance-stabilize the arylnitrenium ion (43) is also important. Arylnitrenium ions that are resonance-stabilized are more mutagenic.

These features are critically dependent on the position of the nitro-substituent.

1.6 The Present work.

This thesis is concerned with an investigation of the reactivity of nitrogen dioxide with appropriate aromatic substrates. It was hoped to obtain further information on the radical/electrophilic nature of nitrogen dioxide as a reagent and it was hoped to obtain some information on the factors influencing the position of radical nitrogen dioxide attack on analogues of environmentally important PAHs.

One initial aim was to investigate the reactions of nitrogen dioxide with the series of 1,2,3-trimethyl-5X-benzene (X = CN, Br, NO_2, phenyl, *t* -butyl and acetate) compounds. This series was chosen for study because the 1,2,3-trimethyl substituent arrangement is known to facilitate electrophilic attack *ipso* to the 2-methyl substituent and because the 5X-substituent was expected to stabilise any cyclohexadienyl radicals. In the event, only the phenyl and the *t* -butyl derivatives were found to react with nitrogen dioxide. These reactions are reported in Chapter 3 and Appendix (B) in this thesis.

As 3,4,5-trimethylphenol was obtained during the preparation of 1-acetoxy-3,4,5-trimethyl-benzene, it was decided to study the reactions of this substrate with nitrogen dioxide. As a result of the results for 3,4,5-trimethylphenol it was decided to extend the study to include 3,4-dimethylphenol and 4-methylphenol. All three of these phenols are unsubstituted at C2 and C6, two ring positions with significant unpaired electron density in the intermediate phenoxy radical. Reactions of such phenols with nitrogen dioxide had not been examined at the onset of this work. This work is reported in Chapter 2.

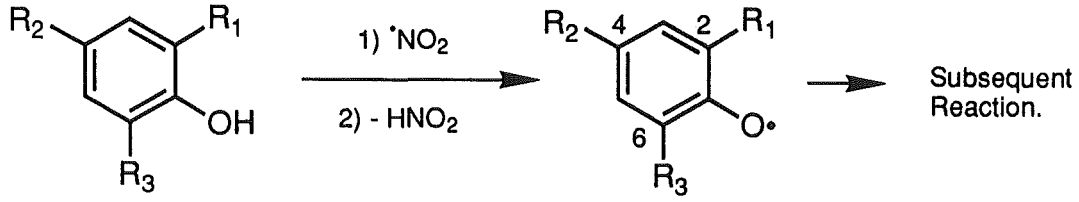
Phenanthrene is the simplest PAH with 'Bay' and 'K' structural features (See Chapter 4), and phenanthrene and its nitrated derivatives are found in environmental samples.[58] Also phenanthrene is reported as giving "unclean" nitration with nitrogen dioxide[63] and it therefore seemed promising to investigate the reactions of this PAH with nitrogen dioxide. The results of this study are reported in Chapter 4.

Chapter 2.

2.1 The Reaction of Phenols with Nitrogen Dioxide.

In Section 1.3.2 the reaction of phenols with nitrogen dioxide was introduced as an example of nitrogen dioxide acting as both an electrophilic and a nucleophilic radical. In this section the reaction of phenols with nitrogen dioxide will be discussed further.

The first step in the reaction of a phenol (44) with nitrogen dioxide involves abstraction of the phenolic hydrogen atom to give a phenoxy radical (45), Scheme 2.1. These delocalised radical species have been shown by electron spin resonance (e.s.r.) spectroscopy to be present as intermediates in the reactions of 2,4,6-tri-*t* -butyl-phenol[64] and 2,6-di-*t* -butyl-4-methylphenol[65] with nitrogen dioxide.



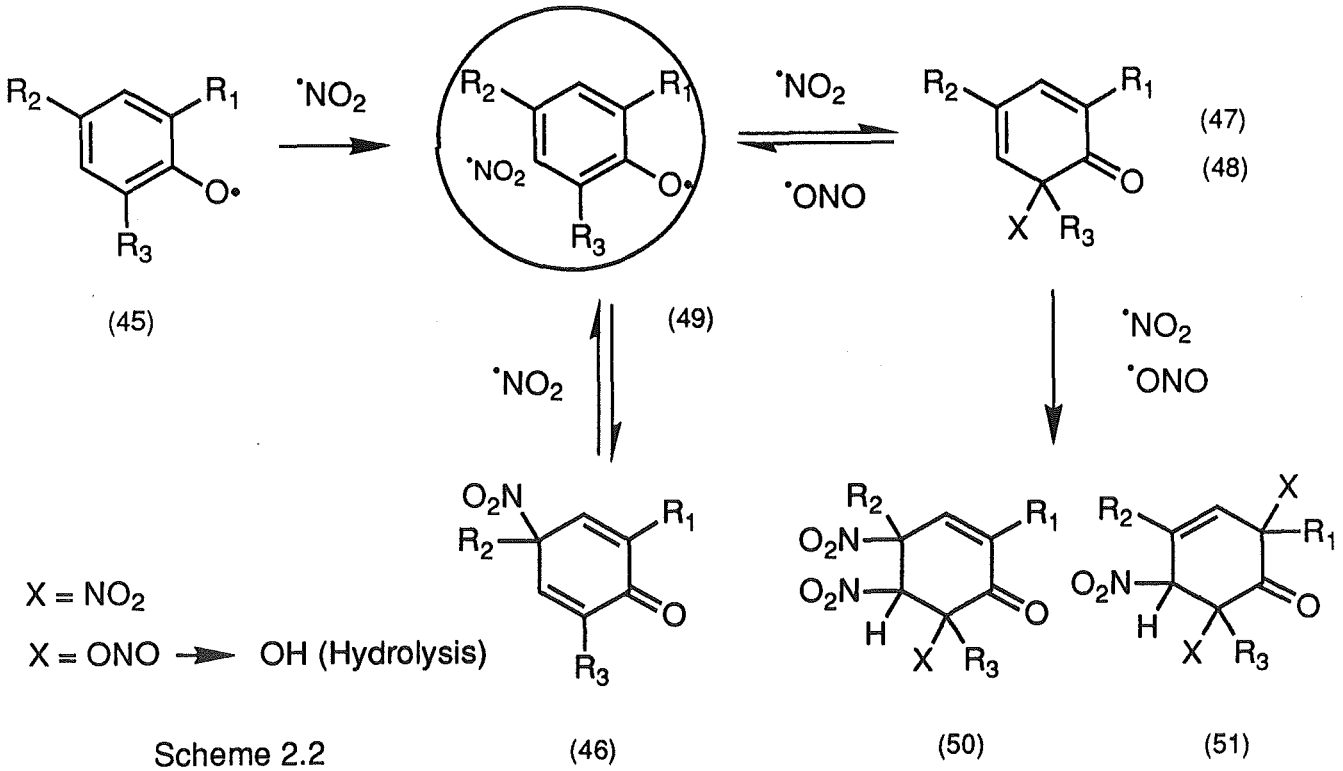
(44) (45)

Scheme 2.1

E.s.r. spectroscopic measurements of phenoxy radicals have been made to determine the distribution of the unpaired electron spin-density on the phenoxy radical.[66] The maximum unpaired electron spin density occurs at the C4 position,with smaller amounts at the C2, C6, C1 positions and on the oxygen atom. There is a "negative" spin-density observed at C3 and C5. The measured unpaired electron spin density at each position on the phenoxy radical is reflected in the products observed following reaction with nitrogen dioxide. Normally it is found that attack by nitrogen dioxide on a phenoxy radical occurs as follows: C4 > C2, C6 >> C1, oxygen >> C3, C5.

The principal reaction of phenoxy radicals is coupling with another unpaired electron species. In a typical reaction with nitrogen dioxide the phenoxy radical (45)

initially gives 4-nitrocyclohexa-2,5-dienone (46) and the 6-nitro (47) and 6-nitrito- (48) cyclohexa-2,4-dienones, Scheme 2.2. The reactive linear dienones, cyclohexa-2,4-dienones (47) and (48), are then the subject of further nitrogen dioxide attack to give: trinitro-, hydroxydinitro-, and dihydroxynitro- cyclohex-2-enones (50) and cyclohex-3-enones (51). The cross-conjugated 4-nitrocyclohexa-2,5-dienone (46) does not react directly with nitrogen dioxide but instead further reaction occurs only *via* a small equilibrium concentration of reactive cyclohexa-2,4-dienones (47) and (48).[35, 36, 67-76]



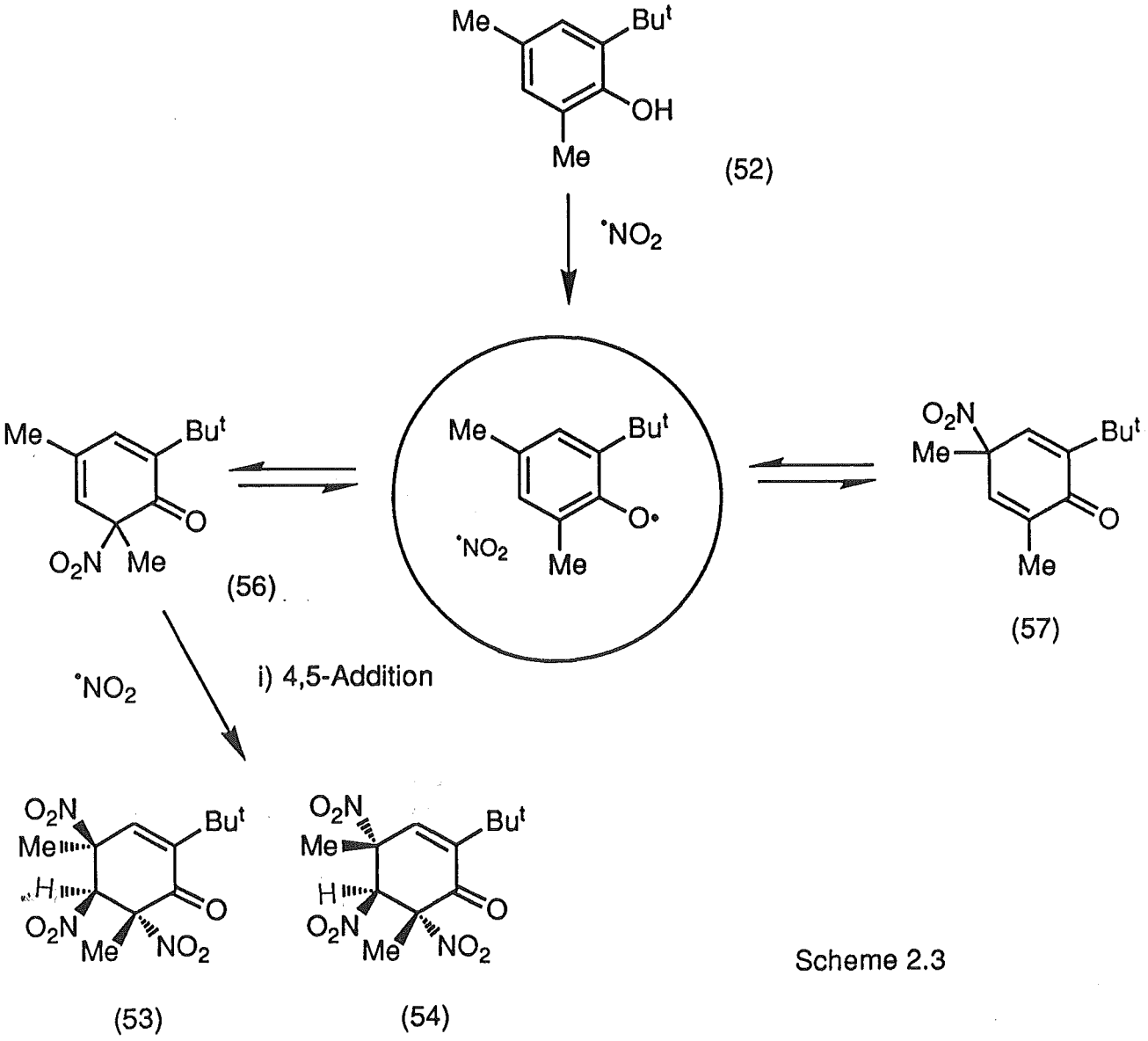
Scheme 2.2

The intermediacy of the radical pair (49) is required to explain the following observations:

(i) rearrangement of the 4-nitrodienone (46) to give 2-nitrodienones (47) is known to occur *via* an intramolecular 1,3-homolytic shift involving a radical pair such as (49),[77, 78] (ii) reaction of the phenol (44) with nitrogen dioxide, and the reaction the of

4-nitrodienone (46) with nitrogen dioxide results in identical product mixtures *i.e.* there has to be a common intermediate such as (49),[34, 67, 69, 71] and (iii) resubmission of ^{15}N-labeled 4-nitrodienone (46) gives products (50) and (51) with the label exclusively in the 6-position, *i.e.* there has been a 1,3 nitro shift taking the ^{15}N-label from the 4- to the 6- position.[74-76]

The 2,4,6- substituted phenols are a group of phenols that have been particularly well studied.[35-37, 67-76] For example, treatment of 2-*t* -butyl-4,6-dimethylphenol (52) with nitrogen dioxide in benzene gave the two C4-epimeric 4,5,6-trinitrocyclohex-2-enones (53) and (54), Scheme 2.3 below.[71] This was seen to be the result of a 4,5-addition of nitrogen dioxide to the 6-nitro-dienone (56) rather than the alternative 5,6-addition to the 4-nitrodienone (57). This reaction has recently been examined in greater detail and the 4,5-addition was confirmed.[74] Resubmission of ^{15}N-labeled 4-nitrodienone (57) gave ^{15}N-labeled trinitrocyclohex-2-enones (53) and (54); the ^{15}N-label was only found at the 6-position consistent with the 4,5-addition pathway shown in Scheme 2.3.


Me
But
OH
Me
(52)
•NO2
Me
But
O2N
Me
(56)
Me
But
O•
•NO2
Me
O2N
Me
But
O
Me
(57)
•NO2
i) 4,5-Addition
O2N
Me
But
H
O2N
Me
NO2
(53)
O2N
Me
But
H
O2N
Me
NO2
(54)

Scheme 2.3

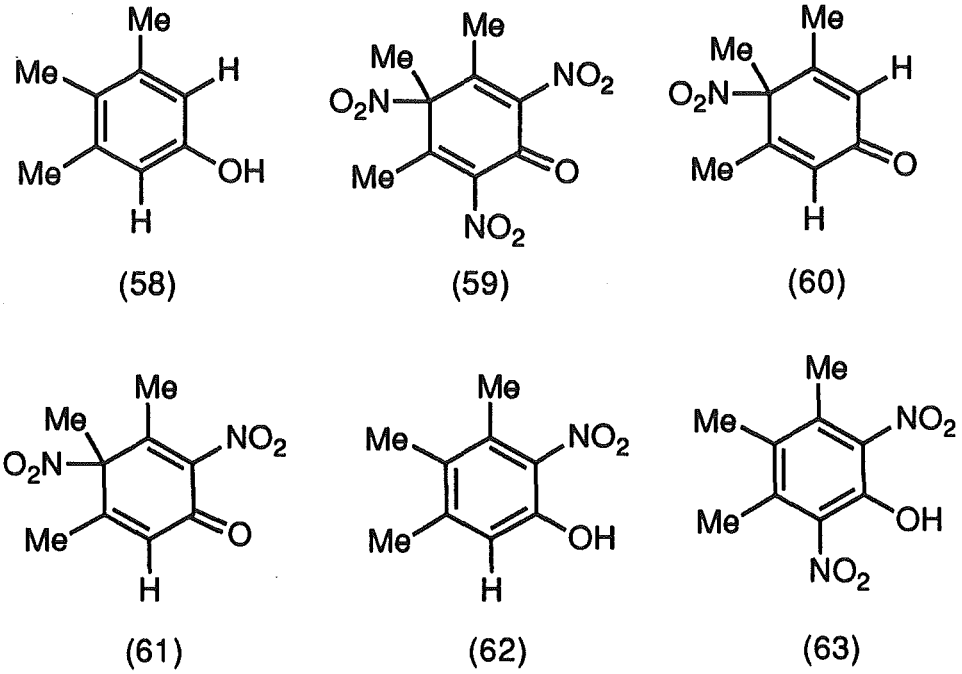
2.2 The Present Work.

The aim of this section of the present work was to investigate the reactions of phenols, unsubstituted at C2 and C6 with nitrogen dioxide in non-polar solvents. At the time this research was started the Fischer and Mathivan paper[79] had not been published and no information on this topic was available.

2.3 The Reactions of 3,4,5-Trimethylphenol (58) and Related Compounds with Nitrogen Dioxide.

2.3.1 The Reaction of 3,4,5-Trimethylphenol (58) with Nitrogen Dioxide in Benzene.

Reaction of 3,4,5-trimethylphenol (58) at < 5° for 1 h gave a mixture (^{1}H n.m.r.) of trinitrocyclohexa-2,5-dienone (59) (29%), nitrocyclohexa-2,5-dienone (60) (39%) and dinitrocyclohexa-2,5-dienone (61) (32%); see Block 2.1 below.



Block 2.1

Trituration of this mixture with cold ether gave the pure trinitrocyclohexa-2,5-dienone (59) as the material insoluble in ether. This compound was assigned the cross-conjugated cyclohexa-2,5-dienone structure (59) on the basis of:

(i) The result of an elemental analysis (Found C, 39.9; H, 3.3; N, 15.0. $C_9H_9N_3O_7$ required C, 39.9; H, 3.4; N, 15.5%) which established a stoichiometry with three nitro substituents.

(ii) The symmetry evident in the ^1H n.m.r. spectra (*c.* δ 2.11, 4-Me; 2.12, 3- and 5- methyls) is consistent with a symmetrical cross-conjugated cyclohexa-2,5-dienone structure. In addition to this, the position (*c.* δ 2.11) of the 4-methyl resonance is within the range, δ 1.90 to δ 2.35, expected for a 4-methyl substituent on a 4-nitro-cyclohexa-2,5-dienone.[80]

(iii) The presence of conjugated ketone (*c.* 1670 cm^{-1}) and nitro (*c.* 1570 cm^{-1}) substituent bands in the infrared spectra.

Chromatography of the ether soluble material on a Chromatotron silica gel plate, gave, in order of elution: nitrophenol (62), dinitrophenol (63), and nitrocyclohexa-2,5-dienone (60).

It is thought that nitrophenol (62) is formed during the isolation procedure. To support this, it will be shown in a later experiment that storage of nitrocyclohexa-2,5-dienone (60) in deuterated chloroform gave nitrophenol (62). A similar rearrangement involving dinitrocyclohexa-2,5-dienone (61) would give dinitrophenol (63).

The first compound eluted, 3,4,5-trimethyl-2-nitrophenol (62), m.p. 100-101° (Lit.[81] 96-98°) is a known compound. It was identified on the basis of the asymmetry apparent in the ^1H n.m.r. spectra (*c.* δ 2.16, 2.30, 2.43, 3-, 4-, 5- methyls; 6.81, H; 9.38, OH) and by the presence of the hydroxyl (*c.* 3410 cm^{-1}) and nitro (*c.* 1514, 1354 cm^{-1}) substituent bands in the infrared spectra.

The second compound eluted was assigned the 3,4,5-trimethyl-2,6-dinitrophenol structure (63) on the basis of the presence of hydroxyl (*c.* 3250 cm^{-1}) and nitro (*c.* 1538 cm^{-1}) substituent bands in the infrared spectra, and because of the symmetry evident in the ^1H n.m.r. spectra (*c* δ 2.27, 4-methyl; 2.39, 2- and 6- methyls; 9.52, OH). In addition to this the elemental analysis (Found C, 47.6; H, 4.8; N, 12.4%) is consistent with the assigned structure.

The third compound eluted, 3,4,5-trimethyl-4-nitrocyclohexa-2,4-dienone (60), m.p. 64.5-66° (Lit.[82] 62.5-64°) is a known compound. It was identified from its spectroscopic data:

(i) The presence of conjugated ketone (*c.* 1682 cm^{-1}) and nitro (*c.* 1549 cm^{-1}) substituent bands in the infrared spectra is consistent with structure (60).

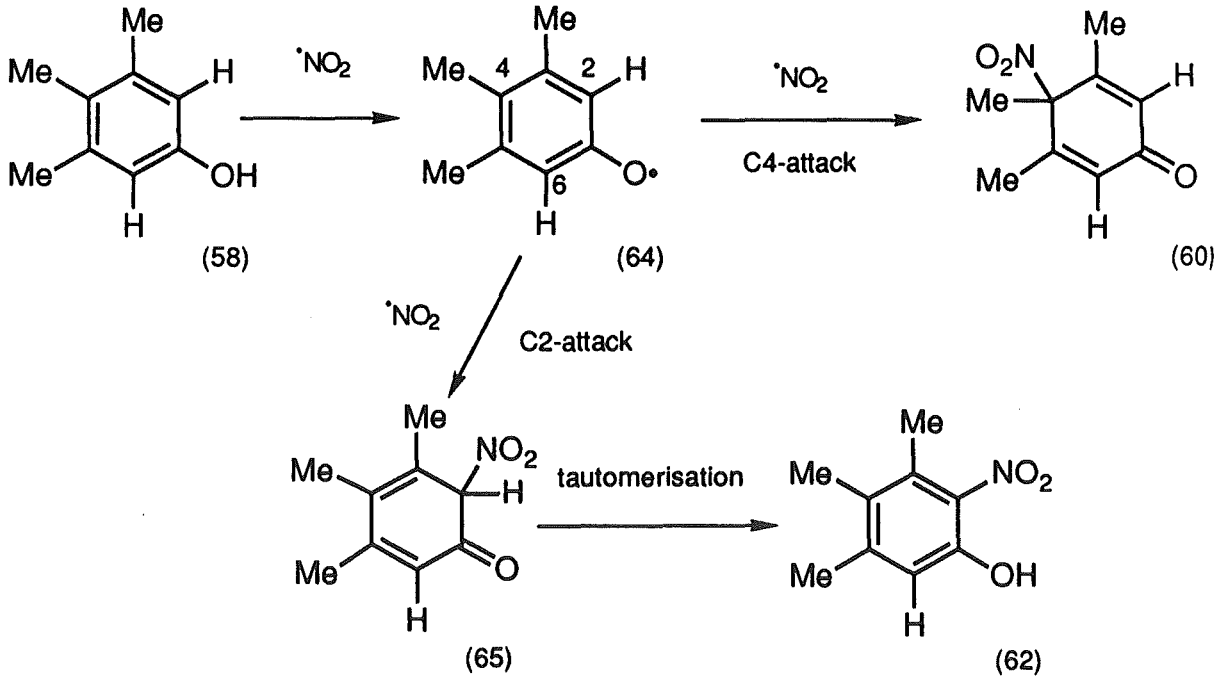
(ii) The ^1H n.m.r. spectra [*c.* δ 1.88, 4-methyl; 1.99, d ($J_{3Me,H2;\ 5Me,H6}$ 1.39 Hz), 3- and 5-methyls; 6.23, m, H2 and H5], exhibits the symmetry and the proton spin-spin coupling pattern expected[83] for structure (60).

3,4,5-Trimethyl-2,4-dinitrocyclohexa-2,5-dienone (61), present in the crude reaction product, was not isolated. The observed ^1H n.m.r. resonances and coupling constants (*c.* δ 1.89, s, 1.99, s, 3-, 4- methyls; 2.02, d, $J_{5\text{-}Me,H6}$ 1.3 Hz, 5-methyl; 6.27, m, H) are consistent with the structure given (61).

Similar reaction of 3,4,5-trimethylphenol (58) with nitrogen dioxide in dichloromethane at < 5° and at -23° in dichloromethane gave similar product mixtures to that described above for 3,4,5-trimethylphenol (58) in benzene.

Under these reaction conditions initial hydrogen abstraction to give the phenoxy radical (64) is followed by coupling of nitrogen dioxide at C4 to yield the isolated 4-nitrodienone (60) which control experiments showed to be stable, Scheme 2.4.

Coupling with nitrogen dioxide at the 2- and 6- positions to give the 6-nitrocyclohexa-2,4-dienone (65) would be followed by rapid tautomerisation to give nitrophenol (62). Although this phenol (62) was not isolated from the reaction of trimethylphenol (58), above, subsequent treatment of nitrophenol (62) with nitrogen dioxide will be shown to give dinitrodienone (61) and trinitrodienone (59), the other products observed from the reaction of trimethylphenol (58) with nitrogen dioxide.

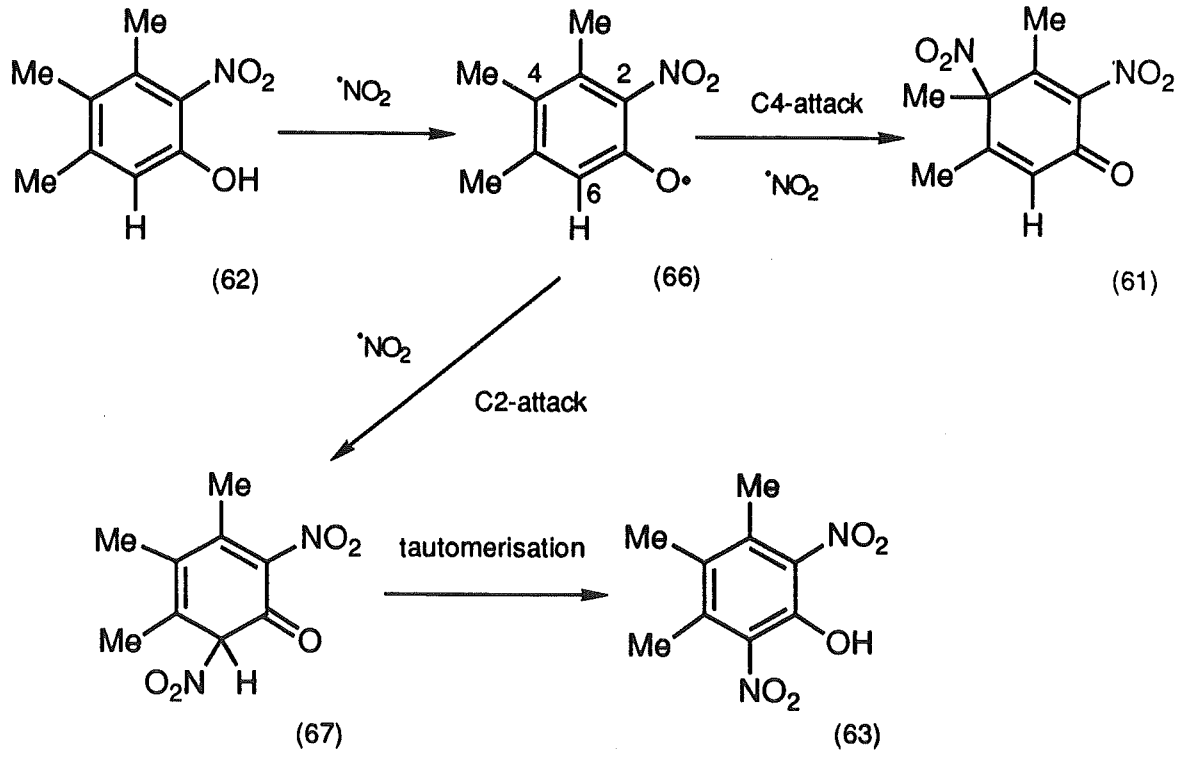


Scheme 2.4

2.3.2 Reaction of 3,4,5-Trimethyl-2-nitrophenol (62) with Nitrogen Dioxide in Benzene.

Reaction of nitrophenol (62) with nitrogen dioxide in benzene at < 5° for 1 h gave a mixture (^{1}H n.m.r.) of trinitrocyclohexa-2,5-dienone (59) (58%) and dinitrocyclohexa-2,5-dienone (61) (42%). Trituration of this mixture with cold ether gave trinitrocyclohexa-2,5-dienone (59) identical with authentic material.

The ether soluble fraction gave, on removal of the solvent under reduced pressure, a residue of trinitrocyclohexa-2,5-dienone (59) (22%) and dinitrocyclohexa-2,5-dienone (61) (78%). Attempts to isolate pure dinitrocyclohexa-2,5-dienone (61) from this mixture were unsuccessful.



Scheme 2.5

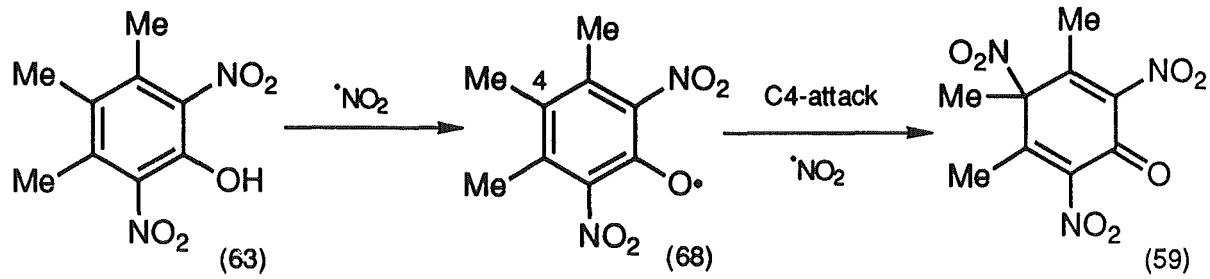
These reactions established nitrophenol (62) as an intermediate on the reaction pathway leading to dinitrocyclohexa-2,5-dienone (61) and trinitrocyclohexa-2,5-dienone (59), Scheme 2.5. The phenoxy radical (66) formed by hydrogen atom abstraction may couple with nitrogen dioxide *either* at C4 to give the dinitrodienone (61) *or* at C6 to give the keto (67) form of dinitrophenol (63). Subsequent reaction of dinitrophenol (63) then gives trinitrocyclohexa-2,5-dienone (59).

2.3.3 Reaction of 3,4,5-Trimethyl-2,6-dinitrophenol (63) with Nitrogen dioxide in Benzene.

Reaction of dinitrophenol (63) with nitrogen dioxide in benzene at < 5° for 1 h gave impure trinitrocyclohexa-2,5-dienone (59). Recrystallisation gave material (59) identical to authentic material.

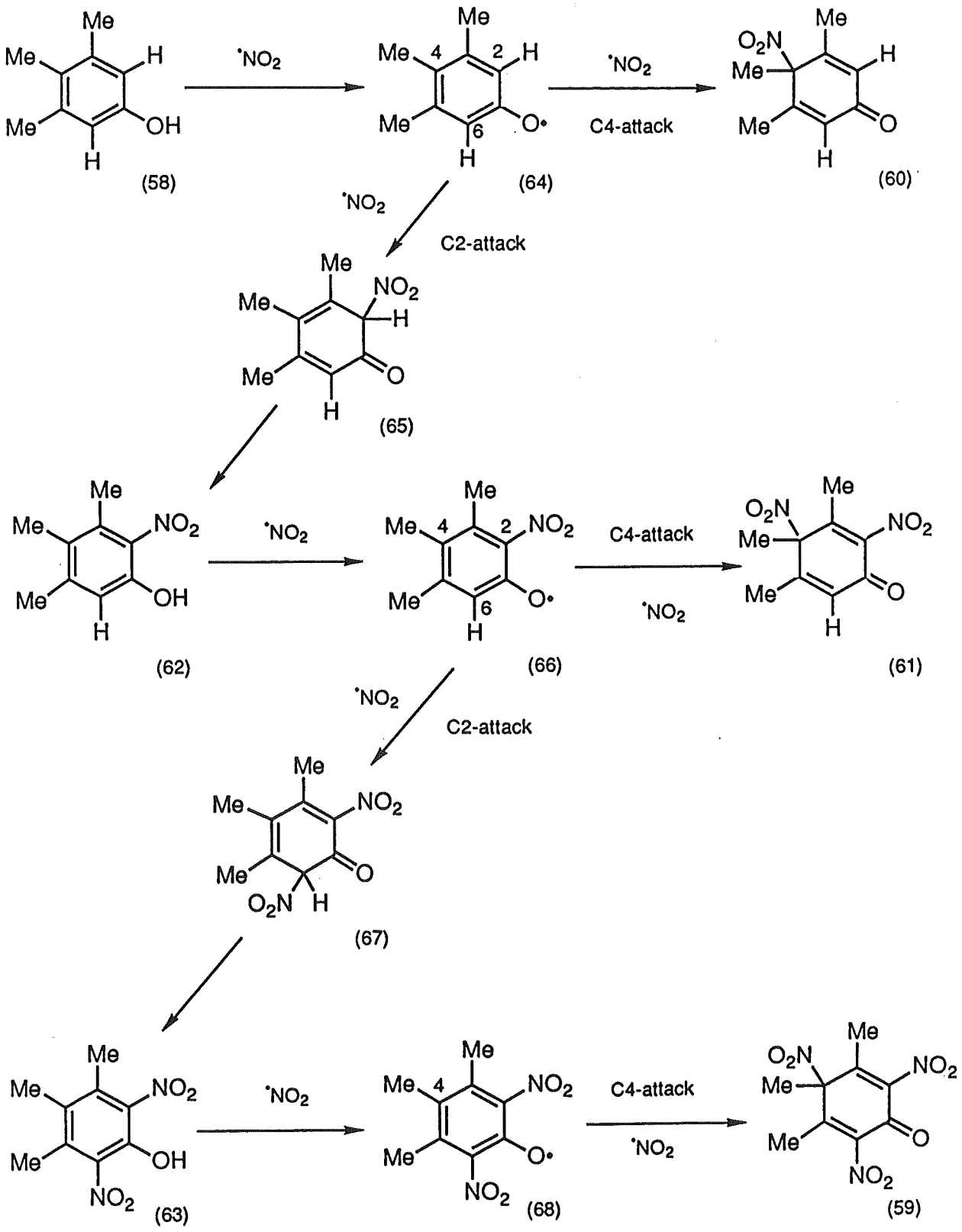
Similar reaction in dichloromethane at -23° gave trinitrocyclohexa-2,5-dienone (59).

This experiment established dinitrophenol (63) as the precursor to trinitrocyclohexa-2,5-dienone (59), Scheme 2.6. Coupling of nitrogen dioxide at the 4-position of the intermediate trimethyldinitrophenoxy radical (68), formed by hydrogen atom abstraction, would give trinitrocyclohexa-2,5-dienone (59).



Scheme 2.6

The overall reaction of 3,4,5-trimethylphenol (63) with nitrogen dioxide is shown in Scheme 2.7. In this reaction the symmetrical phenoxy radical (64), formed by hydrogen atom abstraction, couples with nitrogen dioxide at *either* the 4-position to give nitrocyclohexa-2,5-dienone (60), *or* at the equivalent 2- and 6- positions to give nitrocyclohexa-2,5-dienone (65). This nitro dienone (65) would then tautomerise to give nitrophenol (62). Further reaction of nitrophenol (62) with nitrogen dioxide at the 4-position on the phenoxy radical (66) then gives dinitrocyclohexa-2,5-dienone (61), and attack at the 6-position leads to dinitrophenol (63). The phenoxy radical of this phenol (63) couples with nitrogen dioxide at the 4-position to give trinitrocyclohexa-2,5-dienone (59).


Me
Me
H
Me
OH
H
(58)
•NO2
Me
Me
4
2
H
Me
6
O•
H
(64)
•NO2
C4-attack
Me
O2N
Me
H
Me
O
H
(60)
•NO2
C2-attack
Me
Me
NO2
H
Me
O
H
(65)
Me
Me
NO2
Me
OH
H
(62)
•NO2
Me
Me
4
2
NO2
Me
6
O•
H
(66)
C4-attack
•NO2
Me
O2N
Me
NO2
Me
O
H
(61)
•NO2
C2-attack
Me
Me
NO2
Me
O
O2N
H
(67)
Me
Me
NO2
Me
OH
NO2
(63)
•NO2
Me
Me
4
NO2
Me
O•
NO2
(68)
C4-attack
•NO2
Me
O2N
Me
NO2
Me
O
NO2
(59)

Scheme 2.7

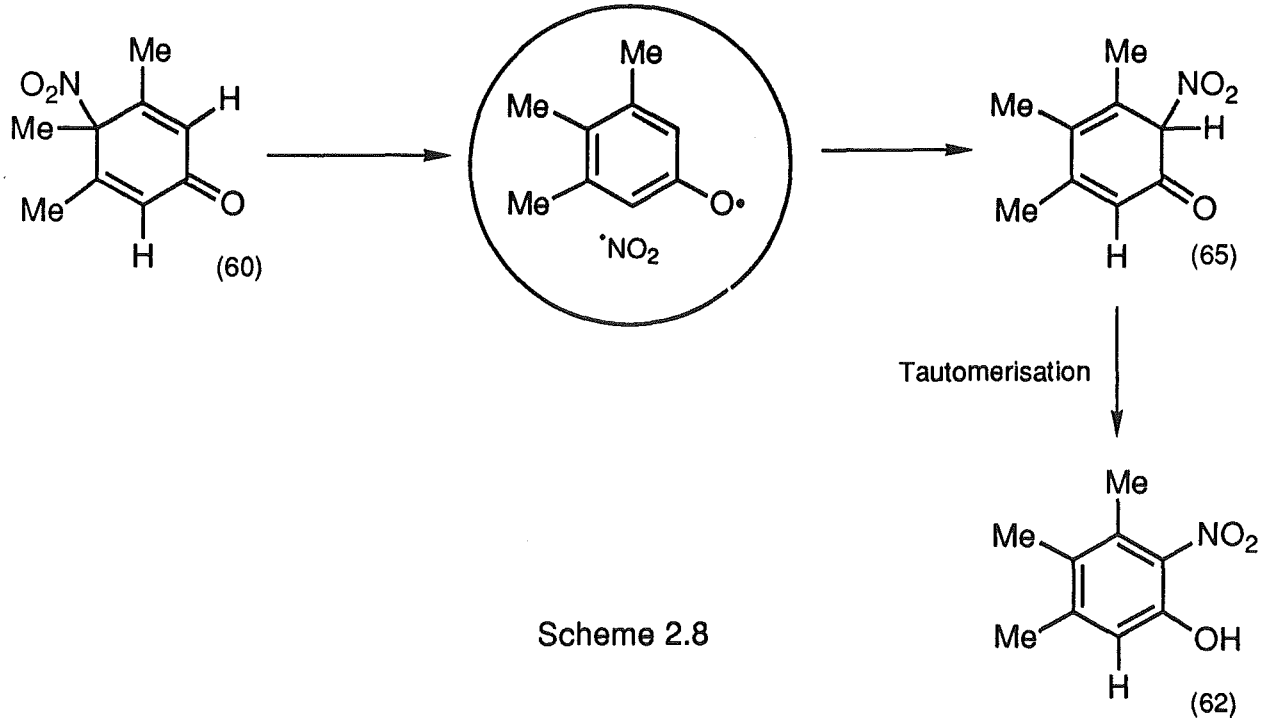
2.3.4 The Isomerisation of 3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) to give 3,4,5-Trimethyl-2-nitrophenol (62).

A solution of nitrocyclohexa-2,5-dienone (60) in deuterated chloroform was stored at 25°. After 48 hours the solution contained a mixture (^{1}H n.m.r.) of the nitrophenol (62) (43%) and the nitrocyclohexa-2,5-dienone (60) (57%). Separation on a Chromatotron silica gel plate gave, in order of elution:

3,4,5-Trimethyl-4-nitrophenol (61), identical with authentic material.

3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (61), identical to authentic material.

The nitrophenol (62) was formed by the reaction pathway shown in Scheme 2.8.



Scheme 2.8

An initial [1,3] nitro group shift by the radical dissociation-recombination mechanism described in Section 2.1 would give 6-nitrocyclohexa-2,4-dienone (65). This rearrangement is followed by tautomerisation to give nitrophenol (62). This type of

isomerisation, (60) → (62), is reported in the literature.[77, 79] It occurs readily in solution at 25°, but slowly at 10° and the nitro dienone (60) is stable at < 5°.

2.3.5 Attempted Reactions of 3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) and 3,4,5-Trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59) with Nitrogen Dioxide.

Treatment of nitrocyclohexa-2,5-dienone (60) with nitrogen dioxide in benzene at < 5° and in dichloromethane at -23° showed no reaction (^{1}H n.m.r.). This experiment established that the cross-conjugated dienone structure (60) is inert to further attack by nitrogen dioxide.

Treatment of trinitrocyclohexa-2,5-dienone (59) with nitrogen dioxide in benzene at < 5° showed no reaction (^{1}H n.m.r.); the cross-conjugated dienone structure (59) is inert to further attack by nitrogen dioxide under these reaction conditions.

2.3.6 The Isomerisation of 3,4,5-Trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59) to give 4-Hydroxy-3,4,5-trimethyl-2,6-dinitrocyclohexa-2,5-dienone (69).

During an early attempt to obtain pure trinitrocyclohexa-2,5-dienone (59) by recrystallisation from dichloromethane/pentane at room temperature a second compound formed slowly. To investigate this reaction further a sample of trinitrocyclohexa-2,5-dienone (59) was dissolved in deuterated chloroform and the mixture was stored at 40° for 24 h. At the end of this time the solvent was removed under reduced pressure to give a colourless solid, which on recrystallisation yielded pure 4-hydroxy-3,4,5-trimethyl-2,5-dinitrocyclohexa-2,5-dienone (69), see Scheme 2.9.

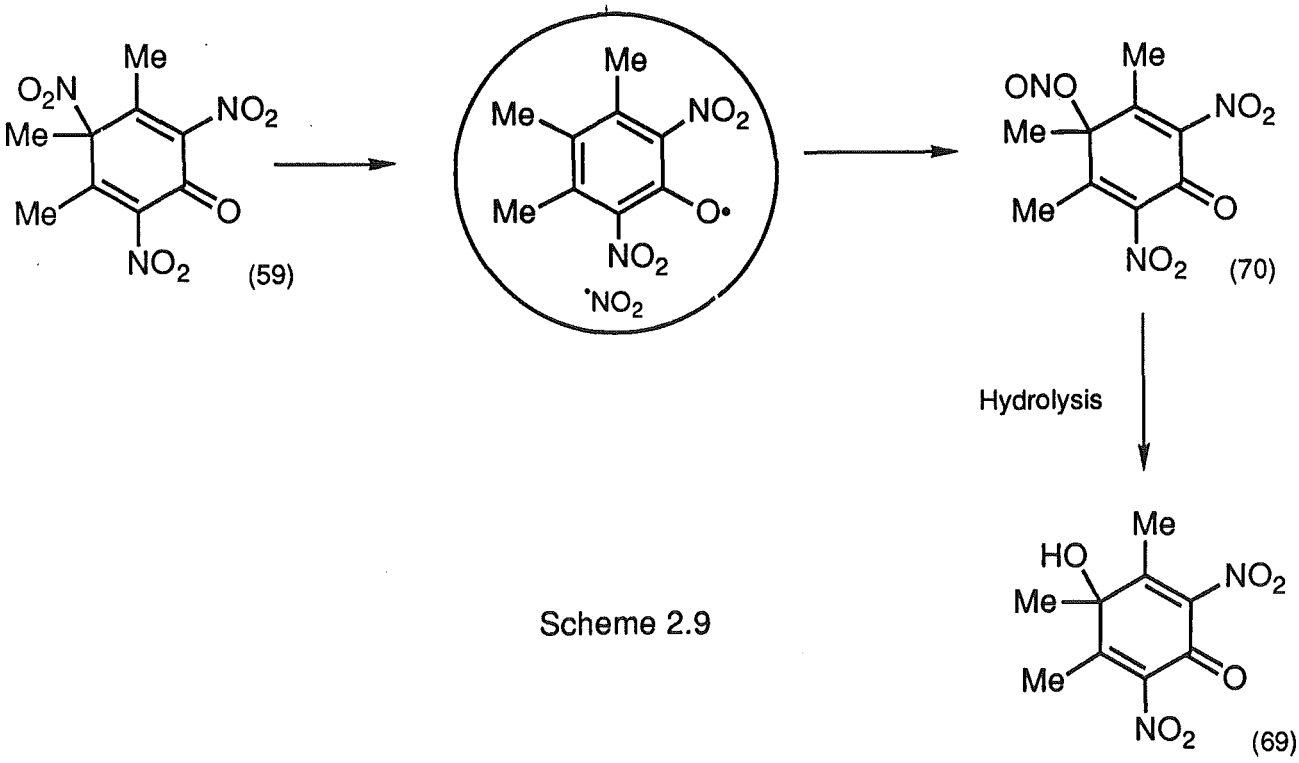
This compound was assigned the 4-hydroxy-3,4,5-trimethyl-2,5-dinitro-cyclohexa-2,5-dienone structure (69) on the basis of:

(i) The presence of the hydroxyl (*c.* 3470 cm^{-1}), conjugated ketone (*c.* 1695 cm^{-1}), and nitro (*c.* 1562 cm^{-1}) substituent bands in the infrared spectra, and

because of the symmetry in the ^1H n.m.r. spectra (*c.* δ 1.67, 4-Me; 2.23, 3- and 5- methyls, 2.49, hydroxyl).

(ii) The high resolution mass spectrum of (69) had a molecular ion $M^{+\bullet}$ 226.058860 ($C_9H_{10}N_2O_5$ = 226.058965).

It is envisaged that 4-hydroxy-2,6-dinitrocyclohexa-2,5-dienone (69) is formed by hydrolysis of the intermediate 4-nitritocyclohexa-2,5-dienone (70), formed by a nitro-nitrito isomerisation *via* the radical pair from trinitrocyclohexa-2,5-dienone (59), Scheme 2.9.



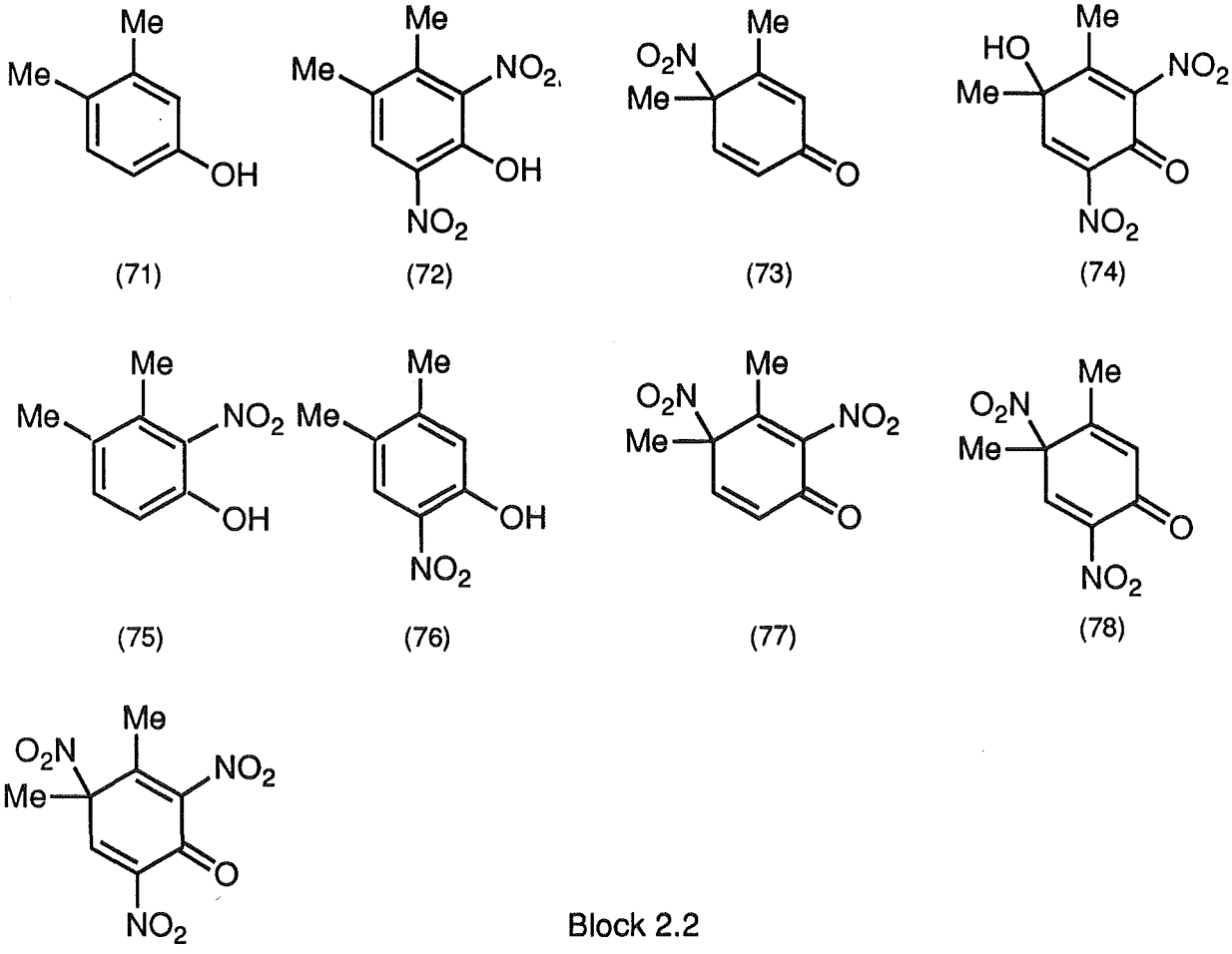
Scheme 2.9

This reaction pathway is analogous to that leading to hydroxy dinitro- and dihydroxy nitro-cyclohexenones (50) and (51), Section 2.1. Examples where similar rearrangements have been proposed to account for the isolation of 4-hydroxycyclohexa-2,5-dienones from 4-nitrocyclohexa-2,5-dienones are found in the chemical literature.[78,80,84]

2.4 Reactions of 3,4-Dimethylphenol (71) and Related Compounds with Nitrogen Dioxide.

2.4.1 Reaction of 3,4-Dimethylphenol (71) with Nitrogen Dioxide in Benzene.

Reaction of 3,4-dimethylphenol (71) with nitrogen dioxide in benzene at < 5° for 1 h gave a mixture (^{1}H n.m.r.) of the three compounds (72) (60%), (73) (29%), (74) (9%), and an unidentified compound (2%), see Block 2.2.



Block 2.2

Chromatography of this material on a Chromatotron silica gel plate gave, in order of elution:

3,4-Dimethyl-2,6-dinitrophenol (72) m.p. 126.5-127.5° (Lit.[85] 126-127°), is a known compound.

It was identified on the basis of the ^{1}H n.m.r. spectra (*c.* δ 2.29, 4-methyl; 2.35, 3-methyl; 8.02, H5; 10.67, hydroxyl) and the presence of hydroxy (*c.* 3230 cm^{-1}) and nitro (*c.* 1542, 1465 cm^{-1}) substituent bands in the infrared spectra.

The second compound eluted, 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73) m.p. 76-77° (dec.) [Lit.[82] 76° (dec.)] is a known compound. This was assigned on the basis of:

(i) The observed ^{1}H n.m.r. resonances and the proton-proton coupling constants [*c.* δ 1.91, s, 4-Me; 2.04, d ($J_{3\text{-Me,H2}}$ 1.4 Hz), 3-Me; 6.27, m, H2; 6.40, d of d ($J_{H6,H5}$ 9.9 Hz, $J_{H6,H2}$ 1.7 Hz), H6; 6.86, d ($J_{H6,H5}$ 10 Hz)] are consistent with the cyclohexa-2,5-dienone structure (73). Of particular importance in the assignment was the position of the 4-methyl resonance (*c.* δ 1.91) within the range, δ 1.90 to δ 2.35, expected for a 4-methyl substituent on a 4-nitrocyclohexa-2,5-dienone structure. The proton-proton coupling constant of 10 Hz between H5 and H6 is typical for a *cis* vinylic system.[83]

(ii) The presence in the infrared spectra of nitro (*c.* 1545 cm^{-1}) and conjugated ketone (*c.* 1664 cm^{-1}) substituent bands.

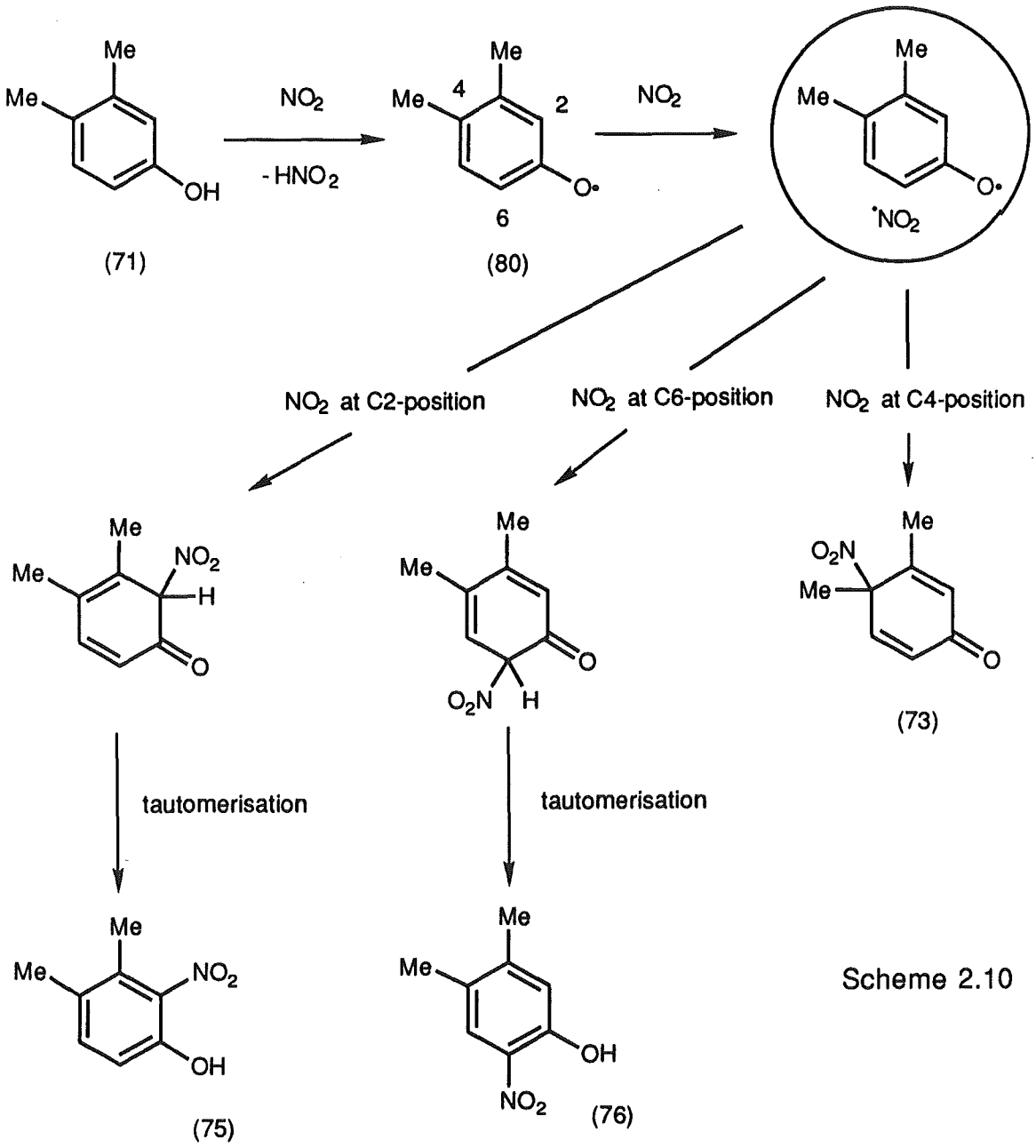
The third compound, 4-hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74), decomposed during the chromatography and was isolated and characterized later.

The unidentified also decomposed and could not be isolated.

Similar reaction of 3,4-dimethylphenol (71) with nitrogen dioxide in dichloromethane at < 5° and in dichloromethane at -23° showed no significant differences from the reaction in benzene.

The 4-nitrodienone (73) is thought to be the product of the reaction pathway shown in Scheme 2.10. The 3,4-dimethylphenoxy radical (80) produced by hydrogen atom abstraction would be expected to couple with nitrogen dioxide at the 2-, 4- and 6- positions to give 3,4-dimethyl-2-nitrophenol (75) and 4,5-dimethyl-2-nitrophenol (76) in addition to the observed product 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73). Although 3,4-dimethyl-2-nitrophenol (75) and 4,5-dimethyl-2-nitrophenol (76) were not isolated from the reaction of 3,4-dimethylphenol (71) above, presumably because the

subsequent reactions were rapid, their reaction with nitrogen dioxide will be shown to give the isolated products (72) and (74).

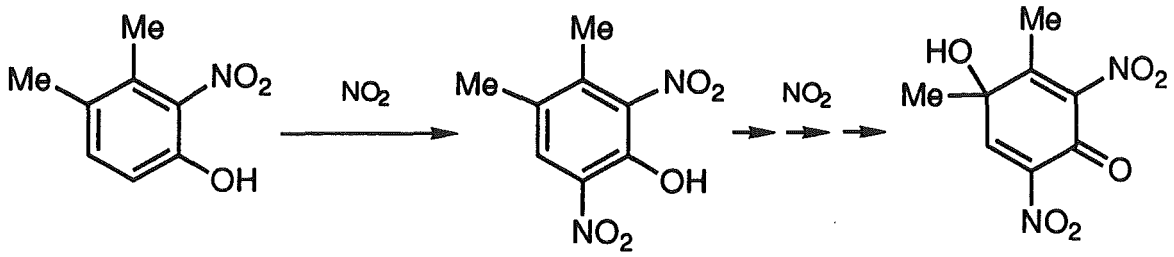


Scheme 2.10

2.4.2 Reaction of 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in Benzene.

Treatment of 3,4-dimethyl-2-nitrophenol (75) with nitrogen dioxide in benzene for 1 h at < 5° gave a mixture (^{1}H n.m.r.) of dinitrophenol (72) (59%), hydroxydinitrocyclohexa-2,5-dienone (74) (32%) and unknown (9%). Similar reaction at -23° in dichloromethane gave essentially pure dinitrophenol (72).

3,4-Dimethyl-2-nitrophenol (75) would be the product of nitrogen dioxide coupling at the 2-position on the 3,4-dimethylphenoxy radical (80) formed by hydrogen abstraction , Scheme 2.10. It is therefore a likely intermediate in the reaction of nitrogen dioxide with 3,4-dimethylphenol (71). That dinitrophenol (72) and 4-hydroxy-2,6-dinitrocyclohexa-2,5-dienone (74) are formed as the result of this reaction established 3,4-dimethyl-2-nitrophenol (75) as an intermediate on the reaction pathway for the formation of dinitrophenol (72) and 4-hydroxydinitrocyclohexa-2,5-dienone (74) from 3,4-dimethylphenol (71), Scheme 2.11. It will be shown that subsequent reaction of dinitrophenol (72) with nitrogen dioxide gives 4-hydroxy-dinitrocyclohexa-2,5-dienone (74). The varying yield of dinitrophenol (72) and hydroxydinitrocyclohexa-2,5-dienone (74) is related to the reaction temperature. At higher temperatures the major product is hydroxydinitrocyclohexa-2,5-dienone (74) whereas at lower temperatures the reaction proceeds only as far as dinitrophenol (72).



(75) (72) (74)

Scheme 2.11

2.4.3 Reaction of 4,5-Dimethyl-2-nitrophenol (76) with Nitrogen Dioxide.

Reaction of 4,5-dimethyl-2-nitrophenol (76) with nitrogen dioxide in benzene at < 5° gave a mixture (^{1}H n.m.r.) of dinitrophenol (72) (71%) and 4-hydroxydinitro-cyclohexa-2,5-dienone (74) (29%), but reaction at -23° in dichloromethane gave essentially pure dinitrophenol (72). Similar reaction in benzene at 20° gave essentially pure 4-hydroxydinitrocyclohexa-2,5-dienone (74) which gave pure material on recrystallisation from dichloromethane/pentane.

This compound was assigned the cross-conjugated cyclohexadienyl structure (74) on the basis of:

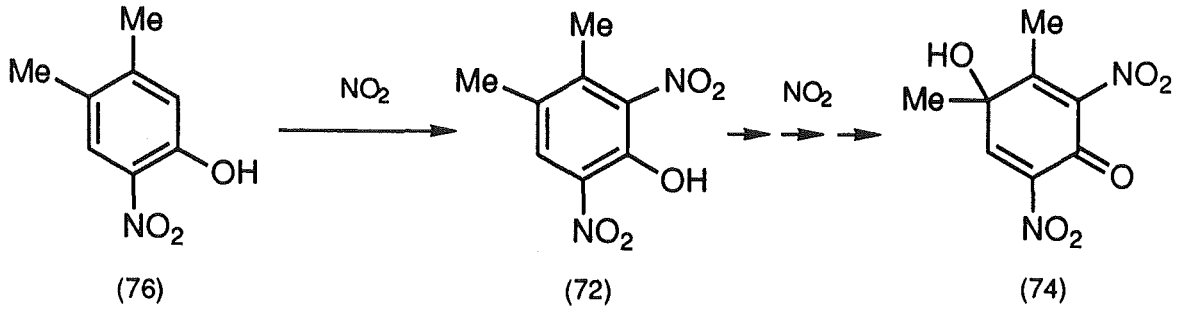
(i) The result of high resolution mass-spectroscopy. The molecular ion $M^{+\bullet}$ was found to have a mass of 228.0381 ($C_8H_8N_2O_6$ = 228.0382).

(ii) The presence of hydroxyl (*c.* 3500 cm^{-1}), conjugated ketone (*c.* 1690 cm^{-1}) and nitro (*c.* 1540 cm^{-1}) substituent bands in the infrared spectra.

(iii) The position of the resonance peaks in the ^{1}H n.m.r. spectra (*c.* δ 1.71, 4-methyl; 2.20, 3-methyl; 7.68, H) is consistent with structure the 4-hydroxydinitro-cyclohexa-2,5-dienone structure (74). In particular the position, δ 1.71, of the 4-methyl resonance is within the range, δ 1.55 to δ 1.85 expected for a 4-methyl on a 4-hydroxy-4-methylcyclohexa-2,5-dienone such as (74).[80]

4,5-Dimethyl-2-nitrophenol (76) is potentially the product of nitrogen dioxide coupling at the 6-position on the 3,4-dimethylphenoxy radical (80) formed by hydrogen abstraction , Scheme 2.10. It is therefore a likely intermediate in the reaction of nitrogen dioxide with 3,4-dimethylphenol (71).

That dinitrophenol (72) and hydroxydinitrocyclohexa-2,5-dienone (74) are formed as the result of this reaction established 4,5-dimethyl-2-nitrophenol (76) as an intermediate on the pathway between 3,4-dimethylphenol (71), and dinitrophenol (72) and 4-hydroxy-dinitrocyclohexa-2,5-dienone (74), Scheme 2.12.

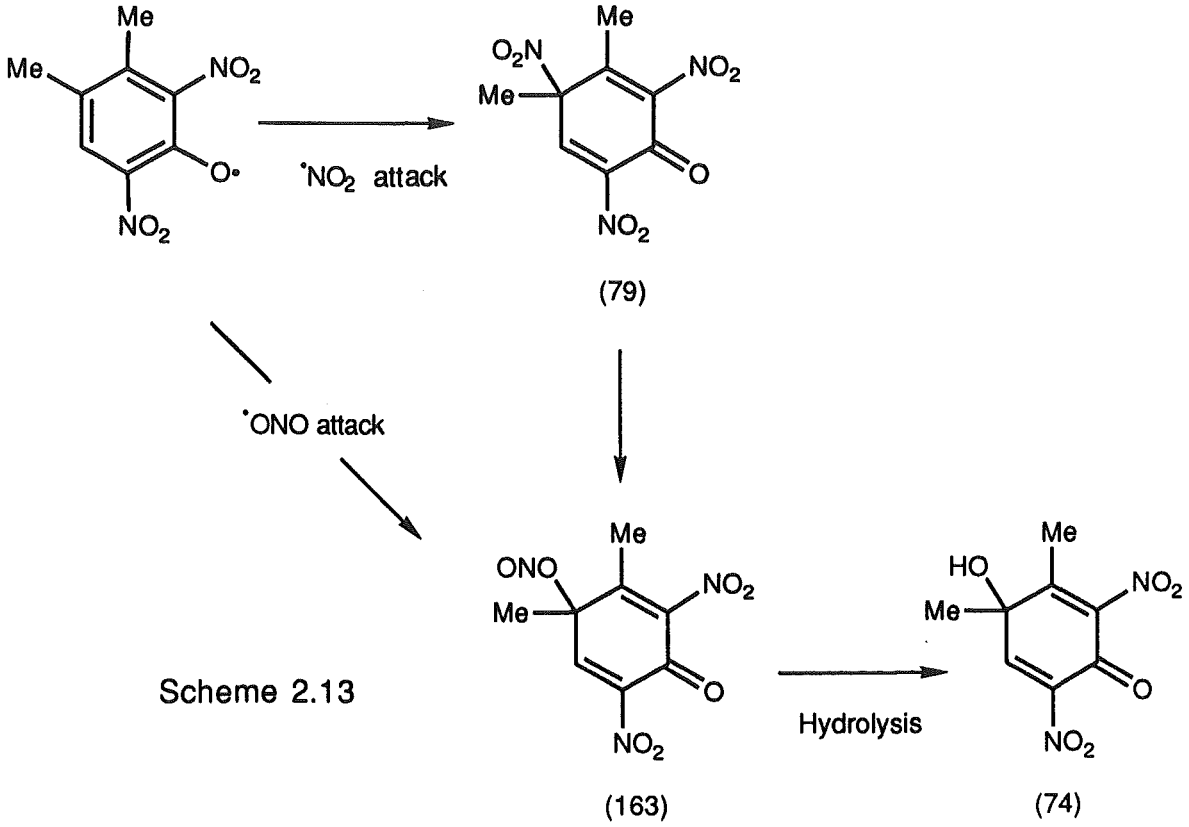


(76) (72) (74)

Scheme 2.12

2.4.4 Reaction of 3,4-Dimethyl-2,6-dinitrophenol (72) with Nitrogen Dioxide in Benzene.

Treatment of 3,4-dimethyl-2,6-dinitrophenol (72) with nitrogen dioxide at < 5° in benzene for 1 h gave a mixture (^{1}H n.m.r.) of dinitrophenol (72) (31%), hydroxydinitrocyclohexa-2,5-dienone (74) (61%), and an unidentified compound (8%). Similar treatment of dinitrophenol (72) with nitrogen dioxide in dichloromethane at -23° gave no reaction.



Scheme 2.13

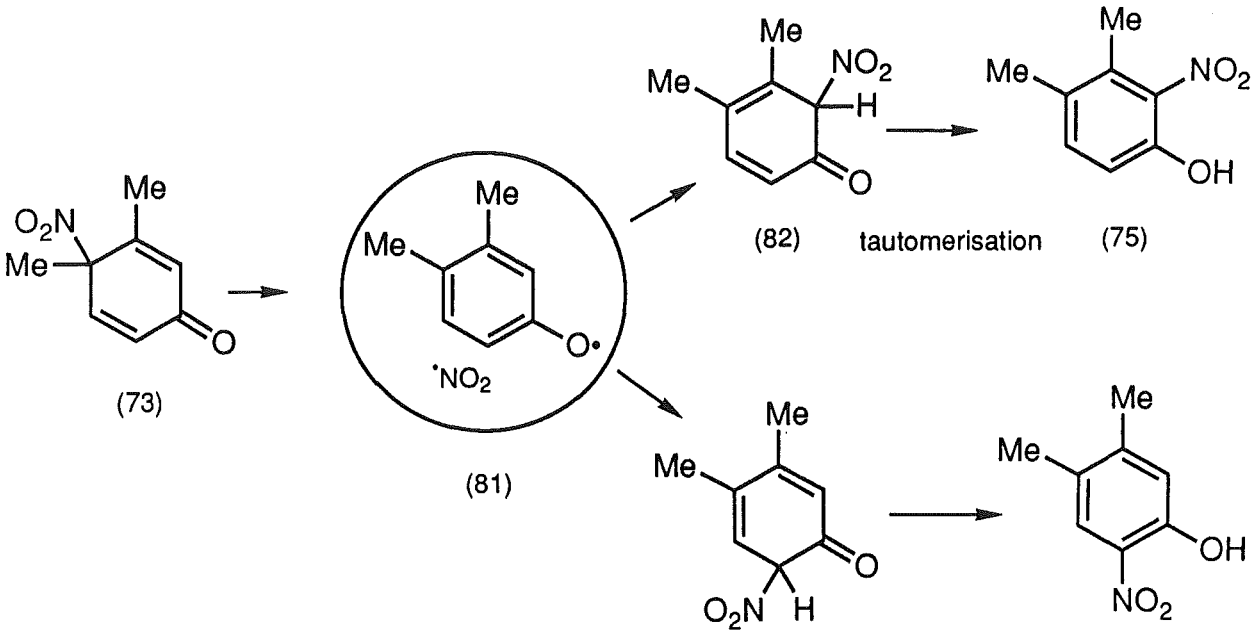
The reaction in benzene at < 5° confirmed that the 4-hydroxydinitrocyclohexa-2,5-dienone (74) is the product of *either* N-centred nitrogen dioxide attack at C4 on the phenoxy radical of dinitrophenol (72) to give the 4-nitro compound (79), followed by rearrangement to give the 4-nitrito-compound (163), *or* it is the result of direct O-centred nitrogen dioxide attack giving the 4-nitritodinitrodienone (163), Scheme 2.13. Subsequent hydrolysis would then give hydroxydinitrocyclohexa-2,5-dienone (74).

2.4.5 Rearrangement of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) in D-Chloroform at 23°.

A solution of nitrocyclohexa-2,5-dienone (73) in deuterated chloroform was stored at 23°. After 22 h the rearrangement was complete and the solution contained a mixture (^{1}H n.m.r.) of 4,5-dimethyl-2-nitrophenol (76) (85%) and 3,4-dimethyl-2-nitrophenol (75) (15%).

The nitrophenols (75) and (76) were formed here by the reaction pathway shown in Scheme 2.14.

An initial [1,3] nitro group shift by the radical dissociation-recombination mechanism described in Section 2.1 would give 6-nitrocyclohexa-2,4-dienones (82) and (83). This rearrangement is followed by tautomerisation to give nitrophenols (75) and (76). This type of isomerisation, (73) → (75) and (76), is reported in the literature[77, 79], it occurs readily in solution at 25°, but it is very slow at 10° and does not occur at < 5°.



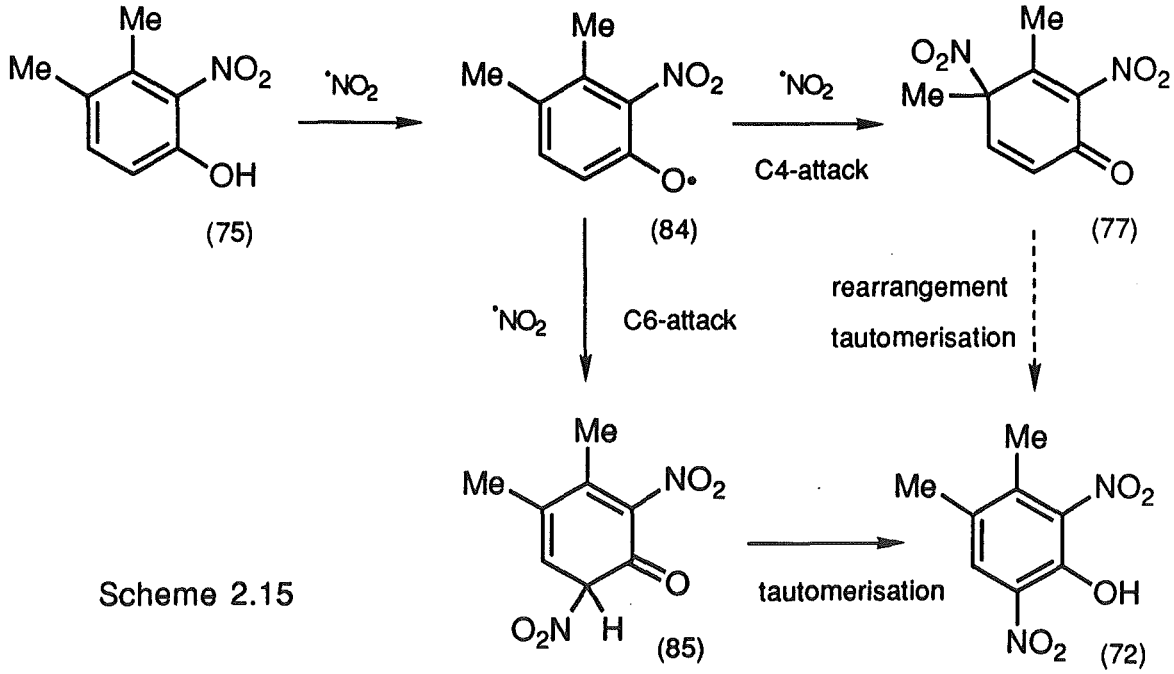
Scheme 2.14

2.4.6 Reaction of 3,4-Dimethyl-2-nitrophenol (75) at -60°.

In this work 3,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77) and 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (78) had not been observed although they are expected products of nitrogen dioxide attack at the 4-position on the phenoxy radicals derived from 3,4-dimethyl-2-nitrophenol (75) and 4,5-dimethyl-2-nitrophenol (76), respectively. We therefore examined the reaction of 3,4-dimethyl-2-nitro-phenol (75) and 4,5-dimethyl-2-nitrophenol (76) with nitrogen dioxide at low temperature following the progress of reaction by ^{1}H n.m.r. spectroscopy.

Treatment of 3,4-dimethyl-2-nitrophenol (75) with nitrogen dioxide in deuterochloroform at -60° in a ^{1}H n.m.r. tube for 5 minutes gave 78% conversion to products shown to be a mixture (^{1}H n.m.r.) of 3,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77) (45%) and 3,4-dimethyl-2,6-dinitrophenol (72) (55%). 3,4-Dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77) was identified by its ^{1}H n.m.r. spectra [*c.* δ 2.09, 2.13, two singlets, methyls; 6.64, d ($J_{H6,H5}$ 10 Hz), H6; 7.09, d ($J_{H5,H6}$ 10 Hz), H5]. 3,4-Dimethyl-2,6-dinitrophenol (72) was also identified by its ^{1}H n.m.r. spectra, identical to authentic material.

The formation of these products, (72) and (77), is envisaged as being the result of the reaction pathway shown in Scheme 2.15. Initial hydrogen atom abstraction by nitrogen dioxide to give the 3,4-dimethyl-2-nitrophenoxy radical (84) would be followed by coupling of nitrogen dioxide at C4 to give 3,4-dimethyl-2,4-dinitrocyclo-hexa-2,5-dienone (77) and by coupling at C6 to give compound (85), the keto tautomer of dinitrophenol (72). It is likely that 3,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77) undergoes rearrangement and tautomerisation to give dinitrophenol (72) at higher temperatures (or during workup) and it was therefore not seen in the earlier reactions.

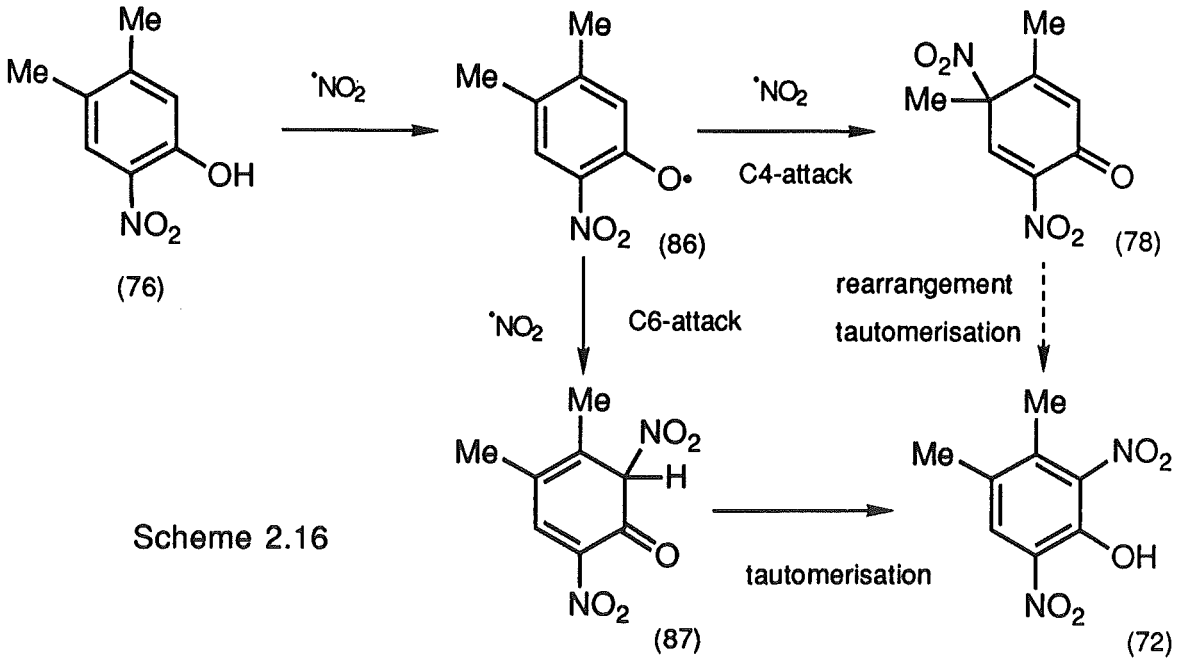


Scheme 2.15

2.4.7 Reaction of 4,5-Dimethyl-2-nitrophenol (76) with Nitrogen Dioxide at -23°.

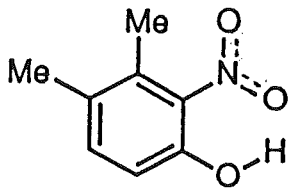
Treatment of 4,5-dimethyl-2-nitrophenol (76) with nitrogen dioxide in deuterochloroform at -60° in a ^{1}H n.m.r. tube resulted in no reaction. Therefore the reaction was repeated at -23° for 1 h. This gave 46% conversion to products shown to be a mixture (^{1}H n.m.r.) of 3,4-dimethyl-2,6-dinitrophenol (72) (58%) (identical with authentic material) and 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (78) (42%), identified by its ^{1}H n.m.r. spectra [*c.* δ 2.09, s, 4-methyl; 2.16, d ($J_{5\text{-Me,H6}}$ 1.4 Hz), 5-methyl; 6.44, q ($J_{H6,5\text{-Me}}$ 1.4 Hz), H6; 7.55, s, H3].

Initial hydrogen atom abstraction by nitrogen dioxide to give the 4,5-dimethyl-2-nitrophenoxy radical (86) would be followed by coupling of nitrogen dioxide at C4 to give 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (78), Scheme 2.16. Coupling at C6 would give compound (87), a keto tautomer of dinitrophenol (72). It is likely that 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (78) undergoes rearrangement and tautomerisation to give dinitrophenol (72) at higher temperatures (or during workup) and was therefore not seen in the earlier reactions.

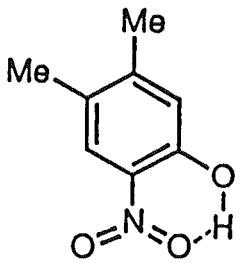


Scheme 2.16

It is interesting that 4,5-dimethyl-2-nitrophenol (76) did not undergo reaction with nitrogen dioxide at -60° whereas 3,4-dimethyl-2-nitrophenol (75) did. This observation is probably the result of the different hydrogen bonding of the two phenols (75) and (76). For reaction to occur the phenolic hydrogen atom must be removed by nitrogen dioxide; in the case of 4,5-dimethyl-2-nitrophenol (76) this would involve breaking the hydrogen bond between the phenolic OH and the adjacent nitro group, Block 2.3. Thus the reaction has a higher activation energy. In contrast, the nitro group of 3,4-dimethyl-2-nitrophenol (75) would be forced from near-coplanarity with the ring and the hydroxyl group by the adjacent 3-methyl group, and intramolecular hydrogen bonding would be absent.



(75)



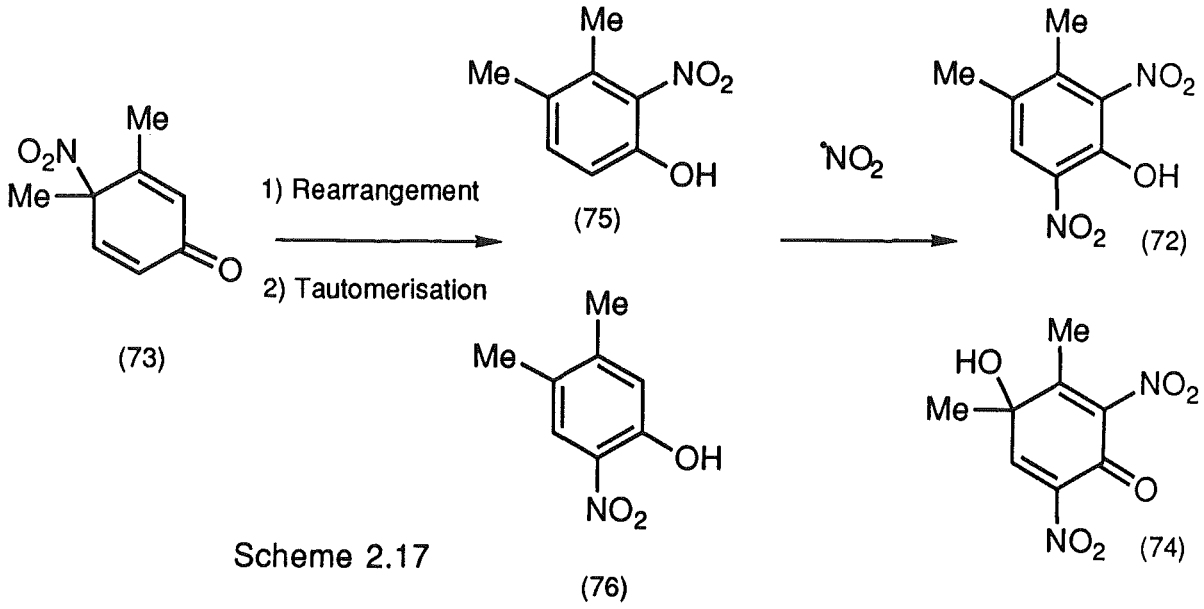
(76)

Block 2.3

2.4.8 Attempted Reaction of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) with Nitrogen Dioxide in Benzene.

Treatment of 4-nitrocyclohexa-2,5-dienone (73) with nitrogen dioxide in benzene at < 5° and in dichloromethane at -23° for 1 h resulted only in recovered 4-nitrocyclohexa-2,5-dienone (73). These experiments show that the cross-conjugated dienone (73) is unreactive to nitrogen dioxide attack under these reaction conditions. However, treatment of nitrocyclohexa-2,5-dienone (73) with nitrogen dioxide in benzene for 1 h at 20° gave a mixture (^{1}H n.m.r.) of dinitrophenol (72) (13%), unreacted nitrocyclohexa-2,5-dienone (73) (53%) and hydroxydinitrocyclohexa-2,5-dienone (74) (34%).

It appears that the dinitrophenol (72) and hydroxydinitrocyclohexa-2,5-dienone (74) formed in the latter experiment are the products of the reaction of nitrogen dioxide with 3,4-dimethyl-2-nitrophenol (75) and 4,5-dimethyl-2-nitrophenol (76), formed as the result of a [1,3] homolytic rearrangement of nitrocyclohexa-2,5-dienone (73). Subsequent reaction of these phenols, (75) and (76), would then give dinitrophenol (72) and hydroxydinitrocyclohexa-2,5-dienone (74), Scheme 2.17.



Scheme 2.17

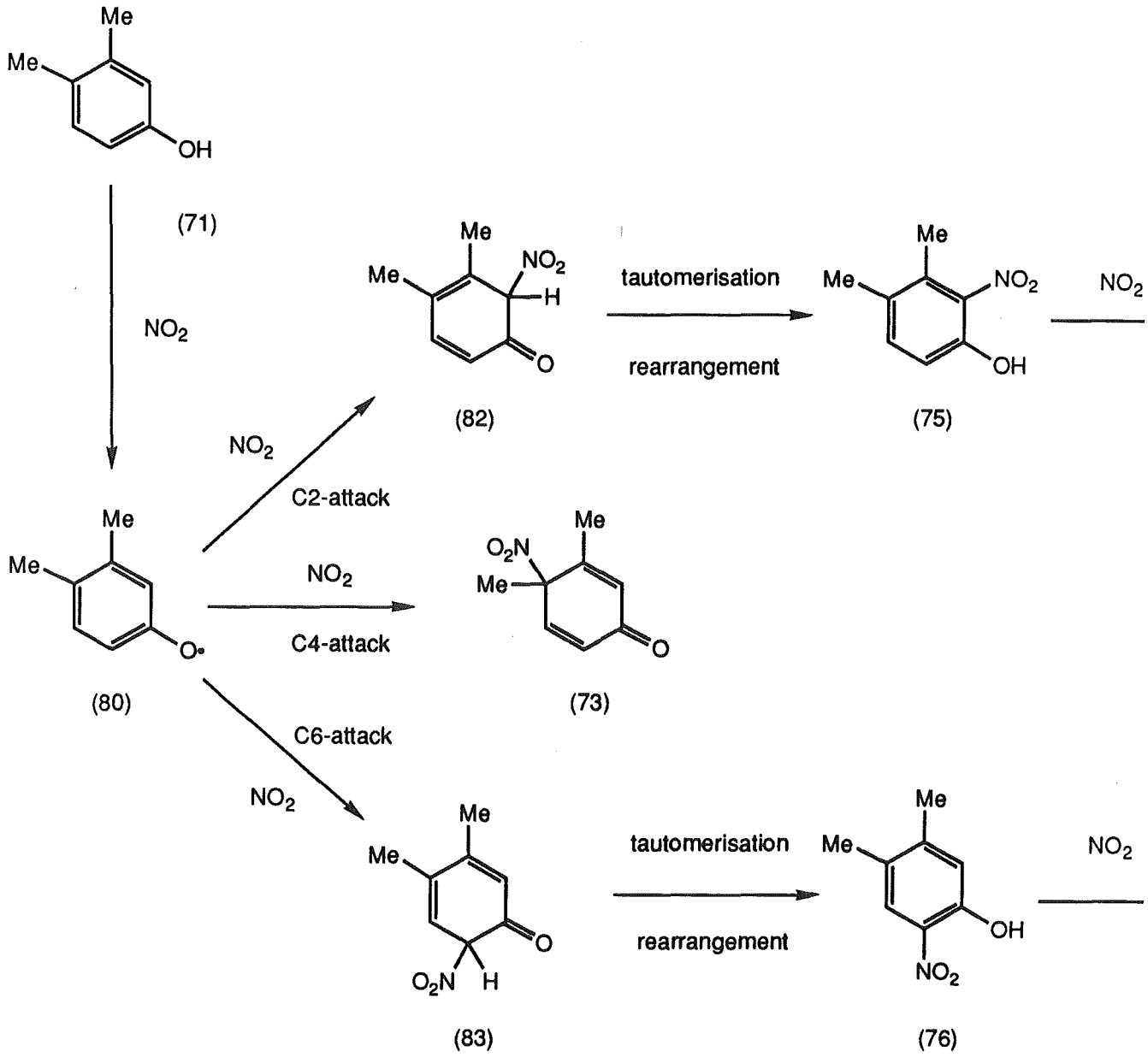
2.4.9 Reaction Pathways in the Reaction of 3,4-Dimethylphenol (71) with Nitrogen Dioxide.

Treatment of 3,4-dimethylphenol (71) with nitrogen dioxide gave dinitrophenol (72), nitrocyclohexa-2,5-dienone (73), and hydroxydinitrocyclohexa-2,5-dienone (74). The probable mode of formation of these compounds is shown in Scheme 2.18.

Hydrogen atom abstraction from 3,4-dimethylphenol (71) would give the 3,4-dimethyl phenoxy radical (80). Subsequent coupling of nitrogen dioxide at C4 would give 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73), a compound which was isolated, and coupling at C2 and C6 would give 4,5-dimethyl-6-nitrocyclohexa-2,4-dienone (82) and 3,4-dimethyl-6-nitrocyclohexa-2,4-dienone (83), respectively. These compounds (82) and (83) are the keto tautomers of 3,4-dimethyl-2-nitro-phenol (75) and 4,5-dimethyl-2-nitrophenol (76), respectively.

The intermediate 3,4-dimethyl-2-nitrophenol (75) and the intermediate 4,5-dimethyl-2-nitrophenol (76) undergo similar reaction. Initial hydrogen atom abstraction to give 3,4-dimethyl-phenoxy radical (84) and 4,5-dimethyl-2-nitro-phenoxy radical (86) is followed by coupling of nitrogen dioxide at C2 and C6. In the case of the 3,4-dimethyl-2-nitrophenoxy radical (84) attack at C4 would give 3,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77) and attack at C6 would give 3,4-dimethyl-

2,6-dinitrocyclohexa-2,4-dienone (85), the keto tautomer of dinitrophenol (72). Similar attack by nitrogen dioxide at C2/C4 and C6 on the 4,5-dimethyl-2-nitro-phenoxy radical (86) would give 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (78) and 4,5-dimethyl-2,6-dinitrocyclohexa-2,4-dienone (87), respectively. All four of these compounds would give dinitrophenol (72). Finally, reaction of dinitrophenol (72) with nitrogen dioxide *via* the dinitrodimethylphenoxy radical gave 4-hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74).

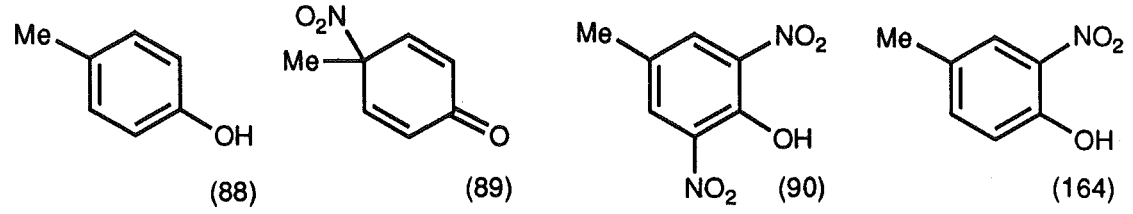


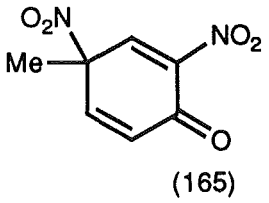
Scheme 2.18

2.5 Reactions of 4-Methylphenol (88) and Related Compounds with Nitrogen Dioxide.

2.5.1 Reaction of 4-Methylphenol (88)with Nitrogen Dioxide.

Reaction of 4-methylphenol (88) at < 5° for 1 h gave a mixture of 4-methylphenol (88) (trace), 4-nitrodienone (89) (23%), and dinitrophenol (90) (77%); see Block 2.4, below.





Block 2.4

Separation on a Chromatotron silica gel plate gave, in order of elution: 4-methylphenol (88) and dinitrophenol (90). The 4-nitrodienone (89) decomposed and it was identified by comparison with its known ^{1}H n.m.r. spectrum.

4-Methyl-2,6-dinitrophenol (90) m.p. 82-83° (Lit.[86] 84°) is a known compound. It was identified on the basis of the symmetry apparent in the ^{1}H n.m.r. spectra (*c.* δ 2.45, 4-methyl; 8.14, H3, H5; 11.28, OH) and by the presence of hydroxyl (*c.* 3100 cm^{-1}) and nitro (*c.* 1530, 1360 cm^{-1}) substituent bands in the infrared spectra.

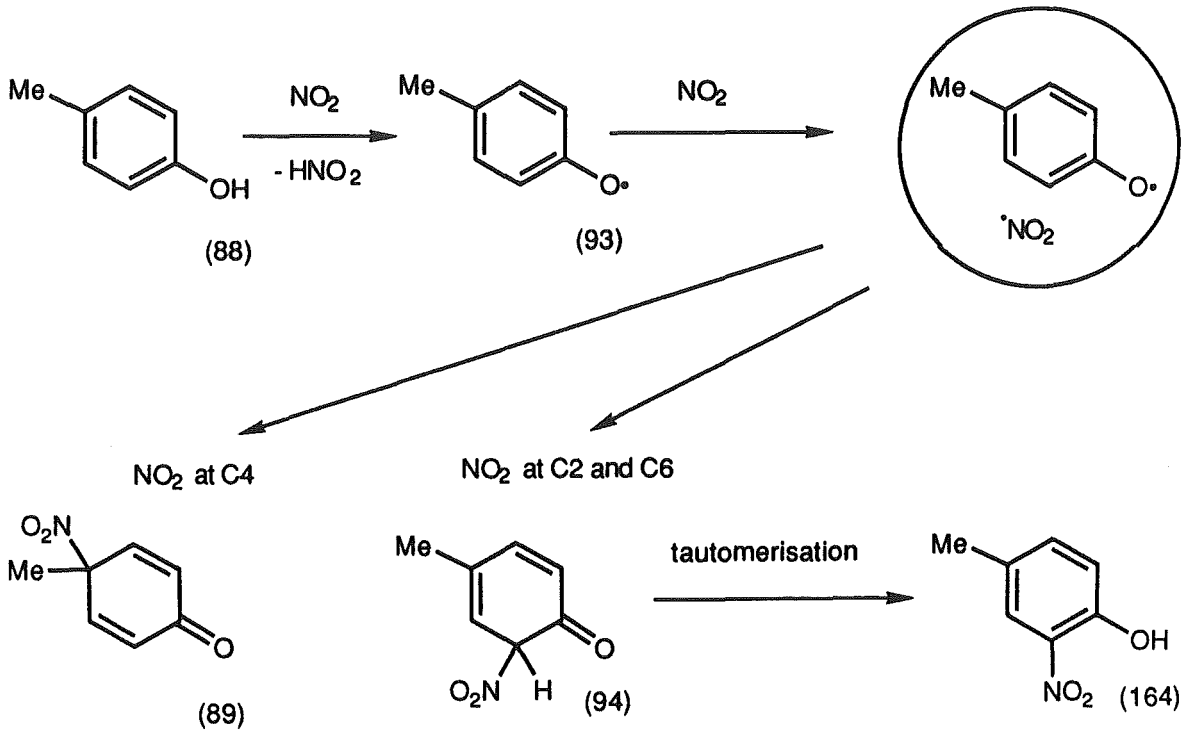
Similar reaction in dichloromethane gave the same products whereas reaction in dichloromethane at -23° gave a small quantity of 4-methyl-2-nitrophenol (164) in addition to 4-nitrodienone (89) and dinitrophenol (90). Separation on a Chromatotron silica gel plate gave:

4-Methyl-2-nitrophenol (164) m.p. 32-33° (Lit.[87] 32-34°) is a known compound. It was identified on the basis of its spectroscopic data:

(i) The presence of hydroxyl (*c.* 3270 cm^{-1}) and nitro (*c.* 1530, 1302 cm^{-1}) substituent bands in the infrared spectra.

(ii) The ^1H n.m.r. spectra [*c* δ 2.35, s, Me; 7.06, d ($J_{H6,H5}$ 8.6 Hz), H6; 7.40, d of d ($J_{H5,H6}$ 8.7 Hz, $J_{H5,H3}$ 2.2 Hz), H5; 7.90, d ($J_{H3,H5}$ 2.2 Hz), H3] is consistent with the proposed structure (164). In particular, the 8.6 Hz coupling constant between H6 and H5 and the 2.2 Hz coupling constant between H3 and H5 are within the ranges expected for *ortho* and *meta* coupling, respectively, on an aromatic ring.[83]

The 4-methylphenoxy radical (93), formed by hydrogen atom abstraction, would be expected to couple with nitrogen dioxide at the 2-, 4-, and 6- positions to give 4-methyl-6-nitrocyclohexa-2,4-dienone (94), the keto tautomer of 4-methyl-2-nitrophenol (164), and 4-methyl-4-nitrocyclohexa-2,5-dienone (89), Scheme 2.19. Both 4-methyl-2-nitrophenol (164) and 4-methyl-4-nitrocyclohexa-2,5-dienone (89) were isolated from the reaction of 4-methylphenol (88) with nitrogen dioxide, and the third product, dinitrophenol (90) will be shown to be a product of the reaction of nitrophenol (164) with nitrogen dioxide.



Scheme 2.19

2.5.2 Reaction of 4-Methyl-2-nitrophenol (164) with Nitrogen Dioxide.

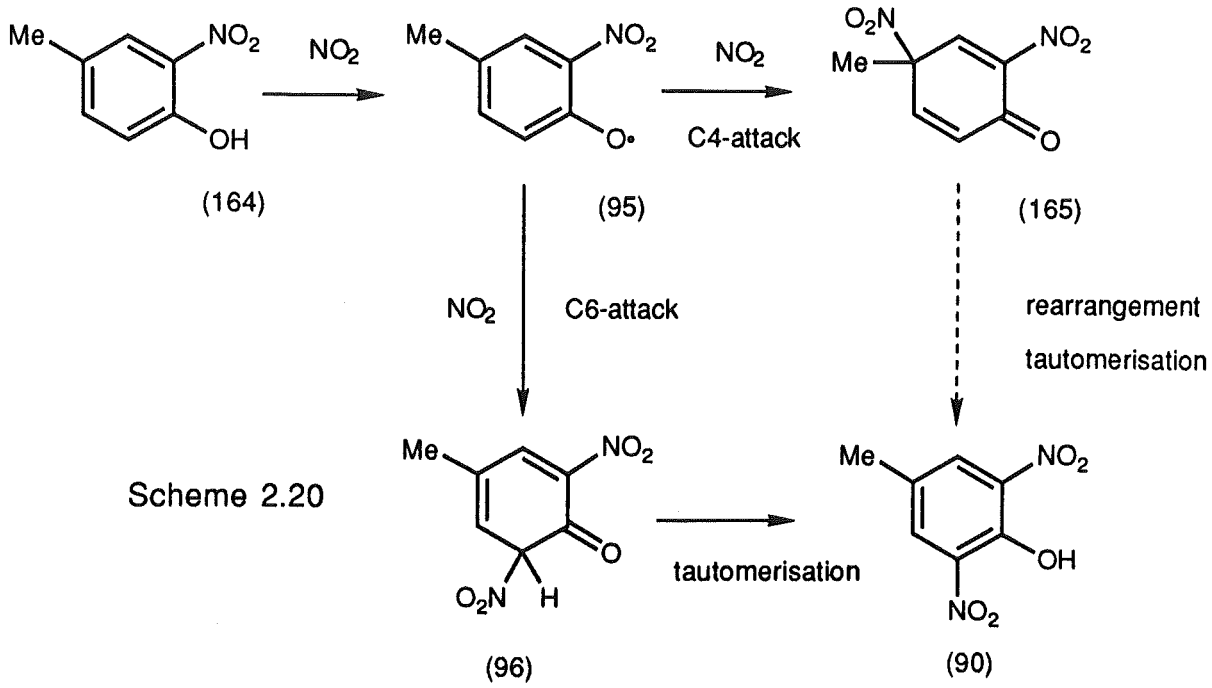
Treatment of 4-methyl-2-nitrophenol (164) in benzene for 1 h at < 5° gave a mixture (^{1}H n.m.r.) of dinitrophenol (90) (92%) and an unknown compound (8%). Similar reaction in dichloromethane at -23° gave dinitrophenol (90) in addition to unchanged nitrophenol (164).

No products of the coupling of nitrogen dioxide at C4 were observed in the reactions above, although we had expected 4-methyl-2,4-dinitrocyclohexa-2,4-dienone (165) to be formed. We therefore examined the reaction of 4-methyl-2-nitrophenol (164) with nitrogen dioxide at low temperature in deuterochloroform following the progress of reaction by ^{1}H n.m.r. spectroscopy. At -60° no reaction occurred. At -23° reaction was slow with only *c.* 46% conversion after 1 h. The major product was 4-methyl-2,6-dinitrophenol (90) (62%), identified by its ^{1}H n.m.r. spectra. The minor product was assigned the 4-methyl-2,4-dinitrocyclohexa-2,4-dienone (165) structure on the basis of the ^{1}H n.m.r. spectra [*c.* δ 2.37, s, 4-Me; 6.57, d ($J_{H6,H5}$ 10 Hz), H6; 7.31, d of d ($J_{H5,H6}$ 10 Hz, $J_{H5,H3}$ 3 Hz), H5; 7.82, d ($J_{H3,H5}$ 3 Hz), H3]. Two features of this ^{1}H n.m.r. spectrum point to the assigned structure (165):

(i) The position of the 4-methyl ^{1}H n.m.r. resonance at δ 2.37 is within the range expected for a 4-methyl substituent on a 4-nitrodienone.

(ii) The 10 Hz coupling constant between H6 and H5 is consistent with a *cis* vinylic system and the 3 Hz coupling constant between H3 and H5, consistent with ω-coupling, points to a structure such as (165).

These experiments established 4-methyl-2-nitrophenol (164) as being on the reaction pathway leading to dinitrophenol (90), Scheme 2.20. Initial hydrogen atom abstraction from nitrophenol (164) to give phenoxy radical (95) is followed by radical coupling with nitrogen dioxide at the 6-position to give 4-methyl-2,6-dinitrocyclohexa-2,5-dienone (96). This compound (96) is the keto tautomer of the isolated dinitrophenol (90). Similar coupling of nitrogen dioxide at C4 would give 4-methyl-2,4-dinitro-cyclohexa-2,4-dienone structure (165). This latter compound was not isolated, presumably because it undergoes rearrangement and tautomerisation to give dinitrophenol (90).



Scheme 2.20

2.5.3 Attempted Reaction of 4-Methyl-2,6-dinitrophenol (90) with Nitrogen Dioxide.

Treatment of 4-methyl-2,6-dinitrophenol (90) with nitrogen dioxide at < 5° in benzene and at -23° in dichloromethane gave only recovered 4-methyl-2,6-dinitrophenol (90). It remains unclear why this phenol (90) fails to give 4-substituted cyclohexa-2,5-dienones in sharp contrast to the reactivity of 3,4,5-trimethyl-2,6-dinitrophenol (63) and 3,4-dimethyl-2,6-dinitrophenol (72).

One possible reason for this failure to react was thought to be that the oxidation potential of the phenol (90) was too small for reaction with nitrogen dioxide to occur. But the calculated oxidation potential of 4-methyl-2,6-dinitrophenol (90) is 1.68 V and the measured oxidation potential of 4-methylphenol (88) is 1.20 V; as higher oxidation potentials favour the initial hydrogen abstraction from the phenol it follows that we would expect reaction to occur more readily in the case of the dinitrated phenol (90).[88] Another possible explanation for the observed non-reaction was that the presence of 2- and 6- nitro substituents could markedly decrease the proportion of the unpaired electron spin density at the four position. However, it is known that substitution on a phenoxy radical has little

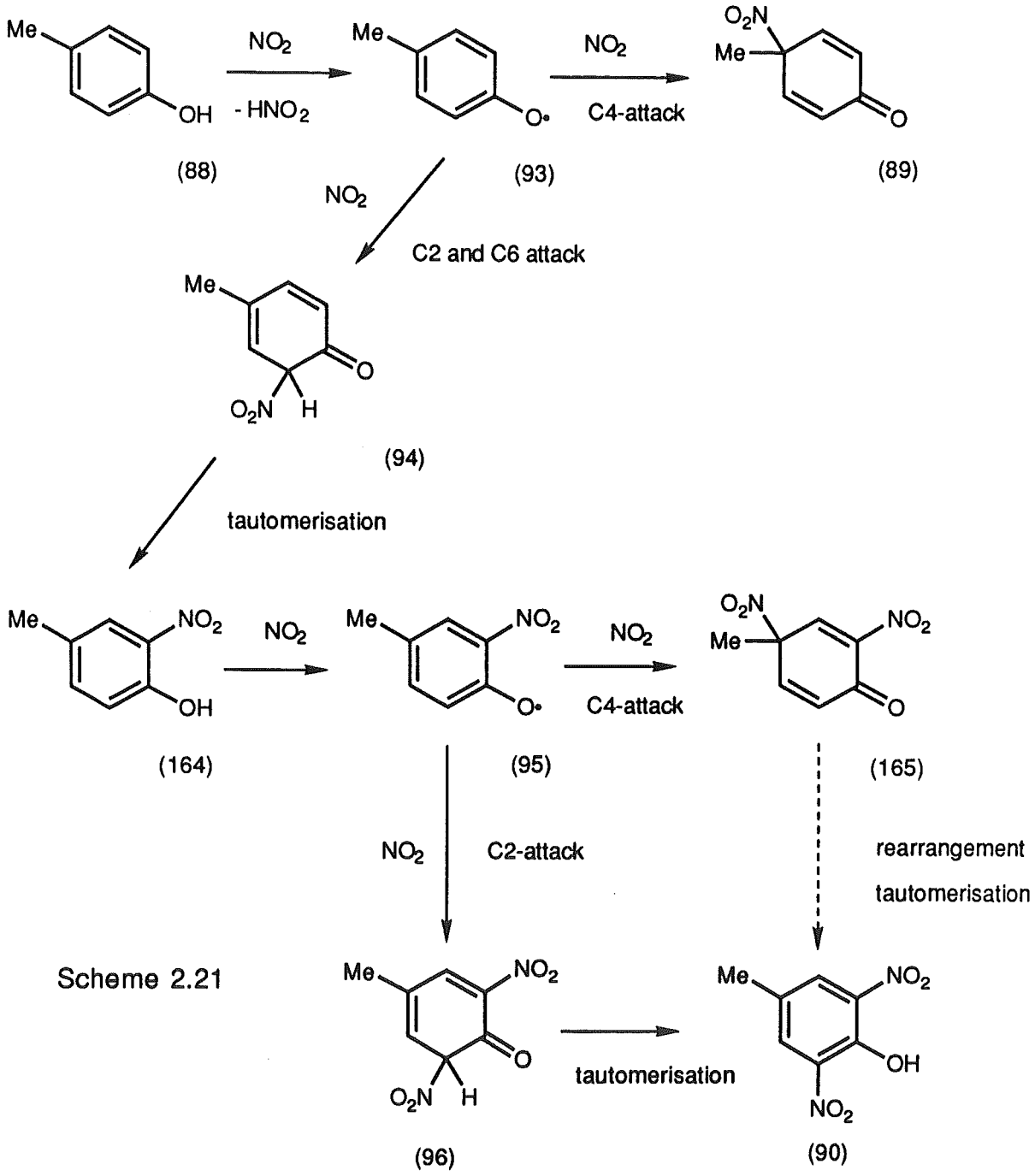
effect on the distribution of the unpaired electron spin density[89-91] so this factor does not account for the observed result either.

2.5.4 Attempted Reaction of 4-Methyl-4-nitrocyclohexa-2,5-dienone (89) with Nitrogen Dioxide.

Treatment of 4-methyl-4-nitrocyclohexa-2,5-dienone (89) with nitrogen dioxide at < 5° in benzene and at -23° in dichloromethane gave only recovered 4-methyl-4-nitro-cyclohexa-2,5-dienone (89). These experiments show that the cross-conjugated dienone (89) is unreactive to nitrogen dioxide attack under these reaction conditions.

2.5.5 Pathways on the Reaction of 4-Methylphenol (88) with Nitrogen Dioxide.

The overall reaction pattern for 4-methylphenol (88) with nitrogen dioxide is shown in Scheme 2.21. The symmetrical phenoxy radical (93) formed by hydrogen atom abstraction couples with nitrogen dioxide at *either* the 4-position to give 4-nitrodienone (89) *or* at the equivalent 2- and 6- positions to give 4-methyl-6-nitrocyclohexa-2,4-dienone (94). This nitro-dienone (94) would tautomerise to give 4-methyl-2-nitro-phenol (164). Further reaction of nitrophenol (164) with nitrogen dioxide *via* the phenoxy radical (95) then gives 4-methyl-2,4-dinitrocyclohexa-2,5-dienone (165), and dinitrophenol (90).

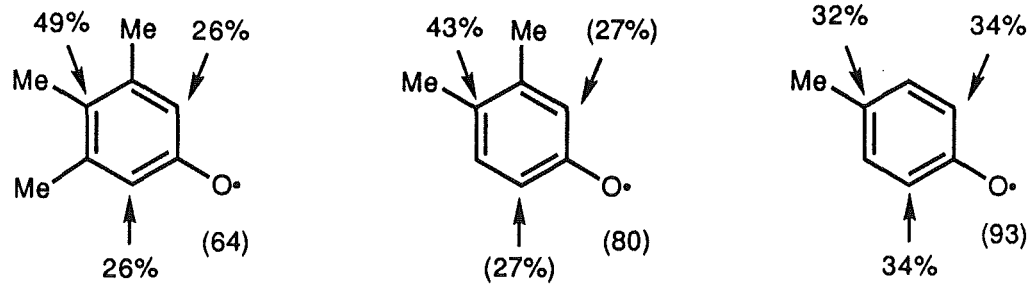


Scheme 2.21

2.6 The Factors Affecting the Partition Between Attack at C4 and, Attack at C2 and C6 for Phenols Unsubstituted at C2 and C6.

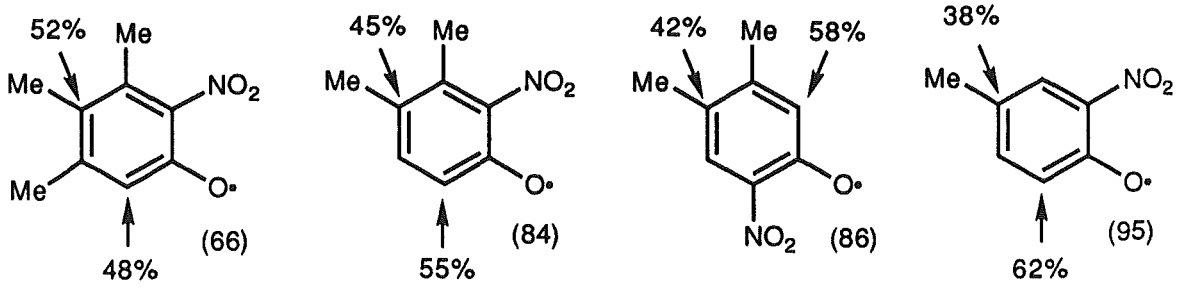
During the investigation, reported above, data on the partitioning between reaction at C4 and reaction at C2 and C6 on the phenoxy radicals formed by hydrogen atom abstraction from a variety of substituted phenols were obtained. In the case of the three

methylphenols (58), (71) and (88) reaction with nitrogen dioxide in dichloromethane at -23° gave the partitioning data shown in Block 2.5. Given the decrease in the proportion of 4-substitution observed it is clear that 3- and 5- methyl substitution favours attack at the 4-position of a phenoxy radical. The significance of this result is emphasized by the observation that the 4-position of the trimethyl phenoxy radical (64) is sterically hindered by the two flanking methyls when compared to the 4-position of methyl phenoxy radical (93). No comment can be made on the partition between the hindered 2- and the unhindered 6- positions of the 3,4-dimethylphenoxy radical (80) because subsequent reaction was rapid and this information could not be obtained.



Block 2.5

The trend away from 4-substitution as the 3- and 4- methyls are removed from the phenoxy radical is also observed when the products of the mono nitrated phenol series are compared. See Block 2.6.



Block 2.6

At first glance it appears that the 2-nitrosubstitution favours 6-attack to give the observed products 2-nitrocyclohexa-2,4-dienones (85) and (87), Scheme 2.18. However, the formation and subsequent rearrangement of *gem.*-dinitrocyclohexa-2,4-dienones

cannot be eliminated as a rapid 1,5-sigmatropic migration of 2-methyl-2-nitrocyclohexa-2,4-dienone is known to give 6-methyl-2-nitrophenol.[92,93]

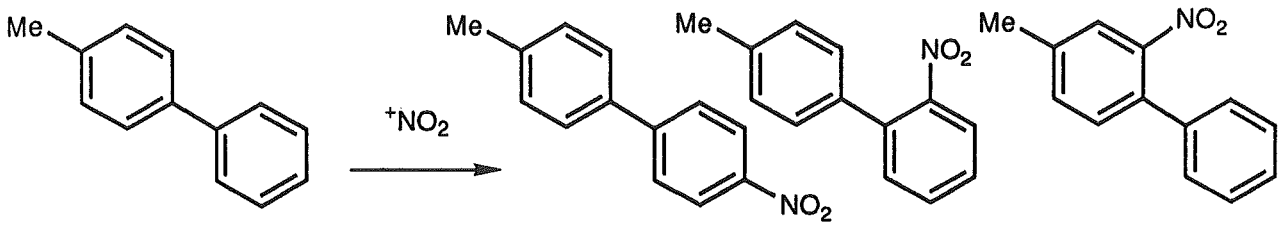
The three dinitrated phenols (63), (72) and (90) gave completely different products when treated with nitrogen dioxide. 3,4,5-Trimethyl-2,6-dinitrophenol (63) initially gave a !00% yield of the 4-nitro-substituted cyclohexa-2,4-dienone (59) which then rearranged and underwent hydrolysis to give the 4-hydroxy-substituted cyclohexa-2,4-dienone (69). 3,4-Dimethyl-2,6-dinitrophenol (72) gave 4-hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,4-dienone (74) in 100% yield by *either* direct oxygen centred $^{\bullet}ONO$ attack, followed by hydrolysis, *or* by nitrogen centred $^{\bullet}NO_2$ attack followed by rearrangement and hydrolysis. In contrast, 4-methyl-2,6-dinitrophenol (90) did not react with nitrogen dioxide. It is unclear why these phenols give different products in the reaction with nitrogen dioxide (See Section 2.5.3 for some relevant comment).

Chapter 3
The Reactions of 3,4,5-Trimethylbiphenyl (91) and 2,3,4-Trimethylbiphenyl (92) With Nitrogen Dioxide.

3.1 Introduction.

One initial aim of this research was to investigate the reactions of the series 1,2,3-trimethyl-5X-benzenes (X = CN, Br, NO_2, phenyl,*t* -butyl and acetate). In this section the results of the reactions of 3,4,5-trimethylbiphenyl (91), 2,3,4-trimethyl-biphenyl (92), and related compounds with nitrogen dioxide will be reported.

Under electrophilic nitration conditions biphenyls typically give a mixture of products, normally with a high level of 4- or 4'- substitution.[94-100] In an early example, Scott *et. al.*[94] treated 4-methylbiphenyl with nitric acid in glacial acetic acid to obtain a mixture of the three mononitrobiphenyls, Scheme 3.1. This example shows a high yield of the 4'-isomer.



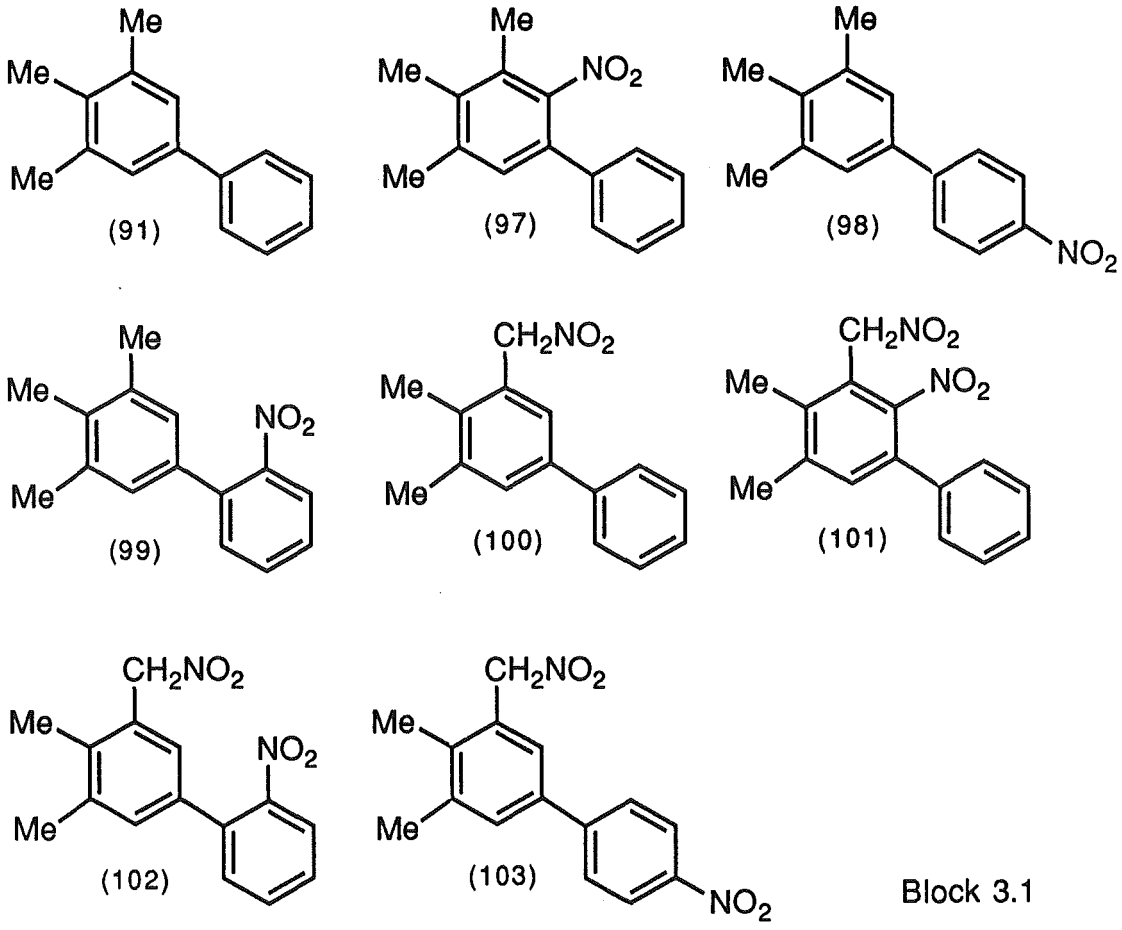
Scheme 3.1

The high proportion of 4- and 4'- substitution observed in the nitration reactions of biphenyls is of particular interest to environmentalists because 4-nitrobiphenyl and 4-,4'-dinitrobiphenyl are known carcinogens, and because it has been shown that the structural features favouring mutagenicity in nitrated biphenyls are the presence of the nitro-group at the 4- position and its absence at the 2-position.[60]

3.2 The Reactions of 3,4,5-Trimethylbiphenyl (91) and Related Compounds with Nitrogen Dioxide.

3.2.1 Reaction of 3,4,5-Trimethylbiphenyl (91) with Nitrogen Dioxide.

Treatment of 3,4,5-trimethylbiphenyl (91) with nitrogen dioxide in benzene at < 5° gave a mixture shown (^{1}H n.m.r.) to contain 2-nitrobiphenyl (97) (46%), 4'-nitrobiphenyl (98) (18%), 2'-nitrobiphenyl (99) (4%), 5-nitromethylbiphenyl (100) (25%), 2-nitro-3-nitromethylbiphenyl (101) (1%), 2'-nitro-5-nitromethylbiphenyl (102) (3%), and 4'-nitro-5-nitromethylbiphenyl (103) (3%), Block 3.1.



Block 3.1

Chromatography of the crude product on a Chromatotron silica gel plate gave, in order of elution:

3,4,5-Trimethyl-2-nitrobiphenyl (97) m.p. 117-118°. This new compound was identified on the basis of:

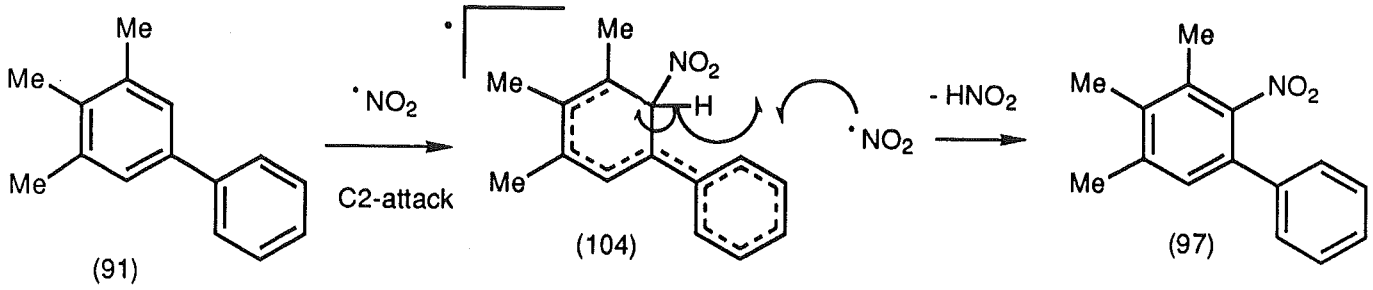
(i) The elemental analysis result (*c.* Found C, 74.3; H, 6.3; N, 5.6. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%); this established a stoichiometry corresponding to one nitro substituent.

(ii) The presence of nitro (*c.* 1523 cm^{-1}) substituent bands in the infrared spectra.

(iii) The ^1H n.m.r. spectra (*c.* δ 2.25, s, 3-Me; 2.27, s, 4-Me; 2.35, s, 5-Me; 7.06, s, H6; 7.36, m, 5 aromatic hydrogens) exhibits the required asymmetry of the three methyl groups and has a singlet of one hydrogen integral (*c.* δ 7.06, s, H6) in the aromatic region upfield to the five hydrogen integral multiplet (*c.* δ 7.36, m, 5 aromatic hydrogens). These features are consistent with the proposed structure (97). In addition, a nuclear Overhauser effect difference spectrum (n.O.e.) where the decoupler position was set at δ 2.35 (*i.e.* 5-methyl) gave positive n.O.e. difference peaks at δ 2.27 (4-methyl) and δ 7.06 (H6) as expected for structure (97) (N.O.e. difference spectroscopy reveals correlations between nuclei that are coupled by dipole-dipole interactions, *i.e.* they are spatially close to one another).[101]

The 2-nitrobiphenyl (97) is the major product from the reaction of 3,4,5-trimethylbiphenyl (91), above. The likely mode of its formation is shown in Scheme 3.2. Initial nitrogen dioxide attack at the C2 position to give the delocalised radical species (104) would be followed by hydrogen atom abstraction by a second nitrogen dioxide molecule to give 2-nitrobiphenyl (97). It is important at this stage to note that the unpaired electron spin density on radical (104) will be located at the substituted C1, C3 and C5 positions on ring one (numbered as for the parent biphenyl) and that delocalisation through the C1-C1' bond would also give unpaired electron spin density at positions C2', C4' and C6'. Significant yields of the 4'- and

2'- nitrobiphenyl (98) and (99) are isolated from this reaction, presumably the result of subsequent nitrogen dioxide coupling at the C2', C4' and C6' positions.



Scheme 3.2

The second compound eluted, 3,4,5-trimethyl-4'-nitrobiphenyl (98) is a new compound. Its structure was determined by a single crystal X-ray analysis. A perspective drawing for this compound, 3,4,5-trimethyl-4'-nitrobiphenyl (98), $C_{15}H_{15}NO_2$, m.p. 110-111°, is presented in Figure 3.1, and the corresponding atomic coordinates are presented in Table A.1. In structure (98), in the crystalline state, the two aromatic rings are staggered with respect to each other as shown by the relevant torsion angle C(2)-C(1)-C(7)-C(12) 31.6°. This observation is important because it indicates a significant resonance interaction between the two aromatic rings of (98) that would also be present in 3,4,5-trimethylbiphenyl (91).[102] The 4'-nitro group lies almost in plane with the phenyl group; torsion angle C(11)-C(10)-N(1)-O(2) 1.1°.

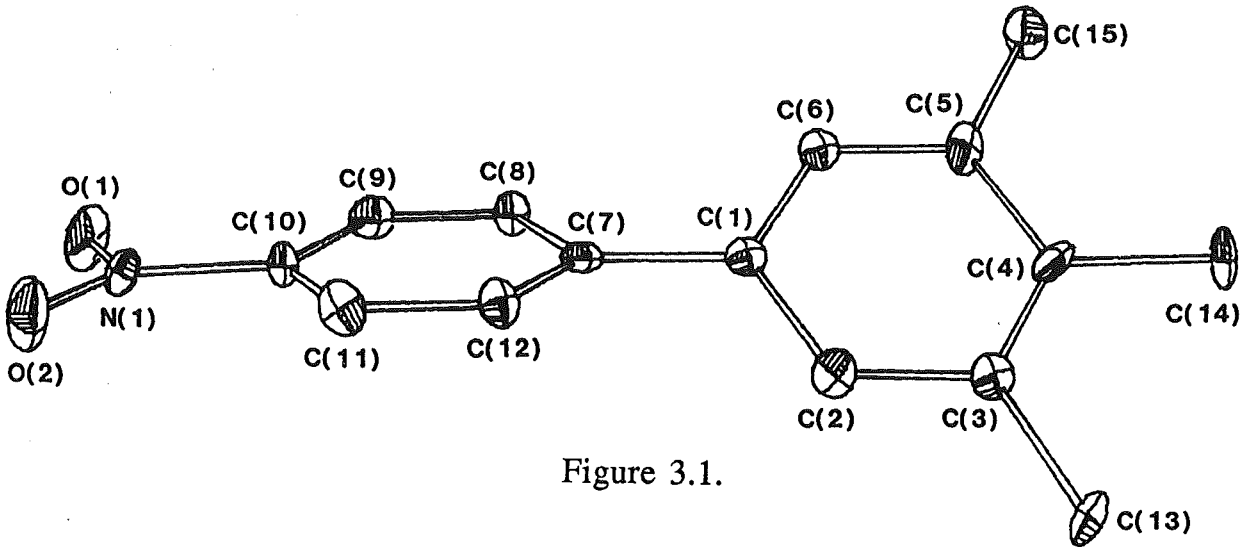


Figure 3.1.

The third compound eluted 3,4,5-trimethyl-2'-nitrobiphenyl (99), m.p. 102.5-103°, was a new compound. Its structure was assigned on the basis of:

(i) The result of an elemental analysis (*c.* Found C, 74.7; H, 6.3; N, 5.7. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%) that established a stoichiometry with one nitro substituent.

(ii) The presence of nitro substituent bands (*c.* 1540, 1340 cm^{-1}) in the infrared spectra.

(iii) The ^1H n.m.r. spectra [*c.* δ 2.21, s, 4-Me; 2.31, s, 3-, 5- methyls; 6.97, s, H2, H6; 7.43, m, H4', H6'; 7.58, triplet of doublets ($J_{H5',H4'}$ 7.55 Hz, $J_{H5',H6'}$ 7.55 Hz, $J_{H5',H3'}$ 1.34 Hz), H5'; 7.80, doublet of doublets ($J_{H3',H4'}$ 8.17 Hz: $J_{H3',H5'}$ 1.56 Hz), H3'], decoupling experiments and the results of the n.O.e. difference experiments support structure (99). That the substitution was on ring two was established because the symmetrical 3,4,5-trimethylphenyl ^1H n.m.r. resonance pattern (*c.* δ 2.21, s, 4-Me; 2.31, s, 3-, 5- methyls; 6.97, s, H2, H6) was still present. The observed splitting pattern of the remaining aromatic hydrogens, *i.e.* two ABC coupling patterns (H3' and H6') and two AB_2C splitting patterns (H4' and H5'), points to 2'-substitution.

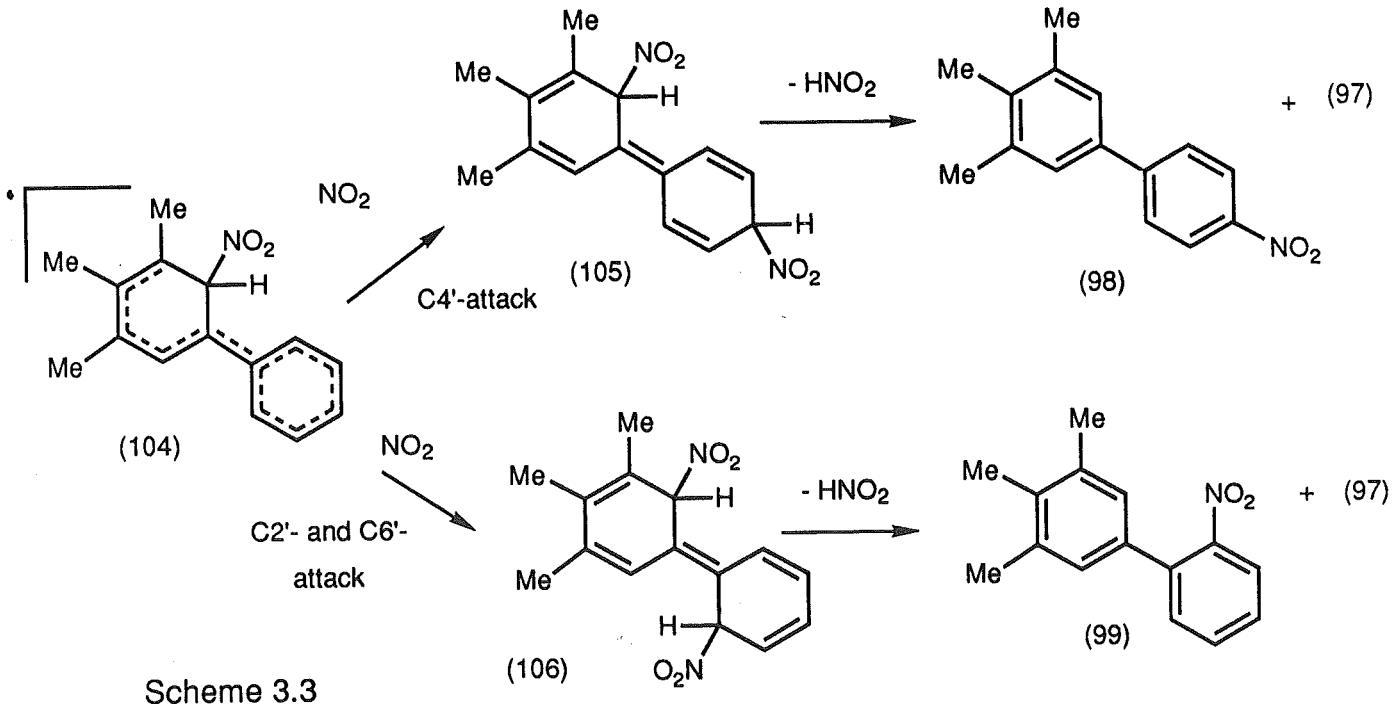
4'-Nitrobiphenyl (98) and 2'-nitrobiphenyl (99) are thought to be formed by the reaction pathway shown in Scheme 3.3. Initial nitrogen dioxide attack at the C2-position to give the delocalised radical species (104), as described above for nitrobiphenyl (97), would be followed by nitrogen dioxide coupling at the unsubstituted positions with significant unpaired electron spin density (C2', C4' and C6') giving the intermediates (105) and (106). Subsequent elimination of nitrous acid would then give 2-, 2'- and 4'- nitrobiphenyls (97), (98) and (99). Reaction is proposed to occur by this addition-elimination mechanism rather than by the addition-hydrogen atom abstraction mechanism described in Scheme 3.2 because biphenyl (107) fails to give nitrated products when treated with nitrogen dioxide under these reaction conditions.

The fourth compound eluted, 4,5-dimethyl-3-nitromethylbiphenyl (100), m.p. 84-85°, was a new compound. It was assigned on the basis of:

(i) An elemental analysis, (*c.* Found C, 74.6; H, 6.3; N, 5.4. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%) consistent with structure (100).

(ii) The presence of a nitro substituent band (*c.* 1543 cm^{-1}) in the infrared spectra.

(iii) The asymmetry apparent in the methyl region of the ^1H n.m.r. spectra (*c* δ 2.32, 4-Me; 2.39, 5-Me) unambiguously locates the nitromethyl-group at the 3-position of the trimethylbiphenyl structure (100) as a nitromethyl-group at position 4-position would give a symmetrical ^1H n.m.r. resonance pattern.



Scheme 3.3

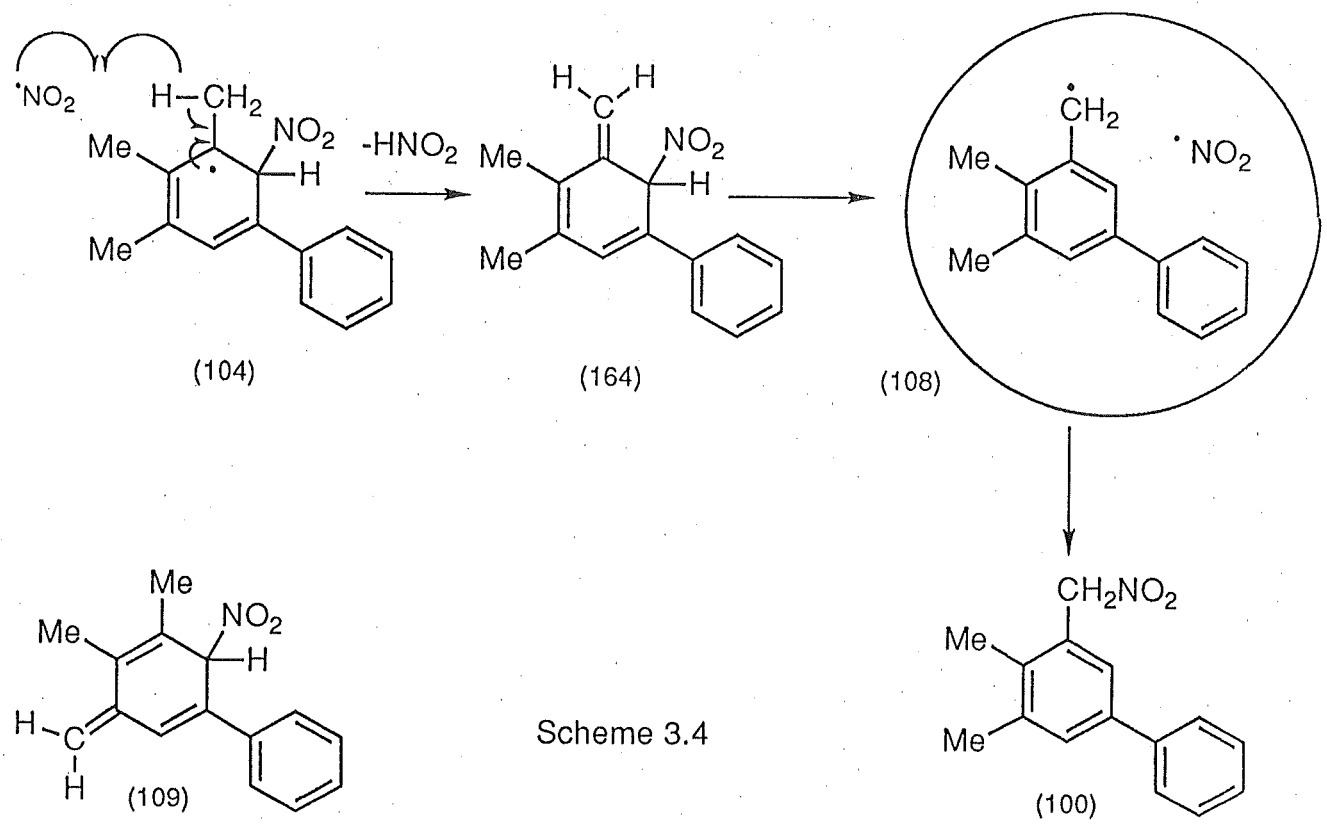
4,5-Dimethyl-3-nitromethylbiphenyl (100) is thought to be the product of the reaction pathway shown in Scheme 3.4. The delocalised radical species (104) formed as the result of nitrogen dioxide attack at C2 on 3,4,5-trimethylbiphenyl (91) would also be the subject of nitrogen dioxide attack at the 3-methyl position giving the exocyclic methylene compound (164). This intermediate (107) would then give the 3-nitromethylbiphenyl (100) *via* the solvent caged radical pair (108). Nitrogen dioxide attack on radical (104) to give the alternative intermediate compound (109) would also give 3-nitromethylbiphenyl (100) *via* (108), this alternative is considered

to be less likely because the presence of the partial negative charge on the nitro-group of (164) would facilitate the approach of the nitrogen dioxide radical necessary to abstract the hydrogen atom.

The fifth compound eluted, 4,5-dimethyl-2-nitro-3-nitromethylbiphenyl (101), m.p. 89-90°, was a new compound. It was assigned structure (101) on the basis of:

(i) The elemental analysis (*c.* Found C, 63.2; H, 5.0; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%) that established a stoichiometry with two nitro substituents.

(ii) The ^1H n.m.r. spectrum (*c.* δ 2.36, s, 4-Me; 2.43, s, 5-Me; 5.55, s, CH_2NO_2; 7.37, s, H6; 7.37, m,5 aromatic hydrogens) and the n.O.e. results support structure (101). Specifically, the peak at δ 5.55 for a nitromethyl substituent and the asymmetry of the remaining methyl groups allows the assignment of the nitromethyl group to the 3-position of the trimethylbiphenyl structure (101). The position of the remaining nitro substituent was determined by n.O.e. experiments. Irradiation at δ 5.55 gave only one positive n.O.e. difference peak (δ 2.36), therefore the nitro group has to be adjacent to the nitromethyl substituent.



Scheme 3.4

The sixth compound eluted, 4,5-dimethyl-2'-nitro-3-nitromethylbiphenyl (102), an oil, was a new compound. It was assigned to structure (102) on the basis of:

(i) Mass spectroscopy (*c.* Found M^- 286.0944. $C_{15}H_{14}N_2O_4$ requires 286.0954) which established a stoichiometry with two nitro substituents.

(ii) The presence in the infrared spectra of nitro substituent bands (*c.* 1525, 1361 cm^{-1}).

(iii) The ^1H n.m.r. spectra [*c.* δ 2.33, s, 4-Me; 2.36, s, 5-Me; 5.55, s, CH_2NO_2; 7.18, s, H2; 7.21, s, H6; 7.49, doublet of doublets ($J_{H6',H5'}$ 7.6 Hz, $J_{H6',H4'}$ 1.6 Hz), H6'; 7.50, triplet of doublets ($J_{H4',H3'; H4',H5'}$ 7.8 Hz; $J_{H4',H6'}$ 1.5 Hz), H4'; 7.66, triplet of doublets ($J_{H5',H4'; H5',H6'}$ 7.6 Hz, $J_{H5',H3'}$ 1.3 Hz), H5'; 7.86, doublet of doublets ($J_{H3',H4'}$ 8.0 Hz, $J_{H3',H5'}$ 1.3 Hz), H3'] that supports structure (102). That the nitromethyl substituent was in the 3-position was established by the asymmetrical ^1H n.m.r. resonance pattern (*c.* δ 2.33, s, 4-Me; 2.36, s, 5-Me; 5.55, s, CH_2NO_2; 7.18, s, H2; 7.21, s, H6). This also placed the second nitro group on ring two of the biphenyl structure (102). The second nitro substituent was placed at the 2'-position because the two ABC coupling patterns (H3' and H6') and the two AB_2C splitting patterns (H4' and H5') apparent in the ^1H n.m.r. spectra are good evidence for this structural feature.

The final compound isolated from the above mixture, 4,5-dimethyl-4'-nitro-3-nitromethylbiphenyl (103), m.p. 120.5-122°, was a new compound. It was assigned structure (103) because of:

(i) An elemental analysis (*c.* Found C, 62.4; H, 4.8; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%) that established a stoichiometry with two nitro substituents.

(ii) Infrared spectra containing nitro substituent bands (*c.* 1564, 1340 cm^{-1}).

(iii) The ^1H n.m.r. spectra [*c.* δ 2.36, s, 4-Me; 2.43, s, 5-Me; 5.60, s, CH_2NO_2; 7.47, s, H2; 7.52, s, H6; 7.73, d ($J_{H2',H3'; H6',H5'}$ 8.9 Hz), H2', H6'; 8.30, d ($J_{H3',H2'; H5',H6'}$ 8.9 Hz), H3', H5'] support this assignment. In particular the asymmetrical ^1H n.m.r. resonance pattern of the ring one methyl substituents

(*c.* δ 2.36, s, 4-Me; 2.43, s, 5-Me) fixes the nitromethyl substituent at the 3-position and, the symmetry of the ring two ^{1}H n.m.r. resonance pattern (an AB quartet with a four hydrogen intergral) places the nitro-substituent unambiguously at the 4'-position.

These final three compounds: 2-nitro-3-nitromethylbiphenyl (101), 2'-nitro-3-nitromethylbiphenyl (102), and 4'-nitro-3-nitromethylbiphenyl (103) will be shown to be the products of the reaction of 3-nitromethylbiphenyl (100) with nitrogen dioxide by reaction mechanisms analogous to those shown in Schemes 3.2, 3.3 and 3.4 above. See Section 3.2.2.

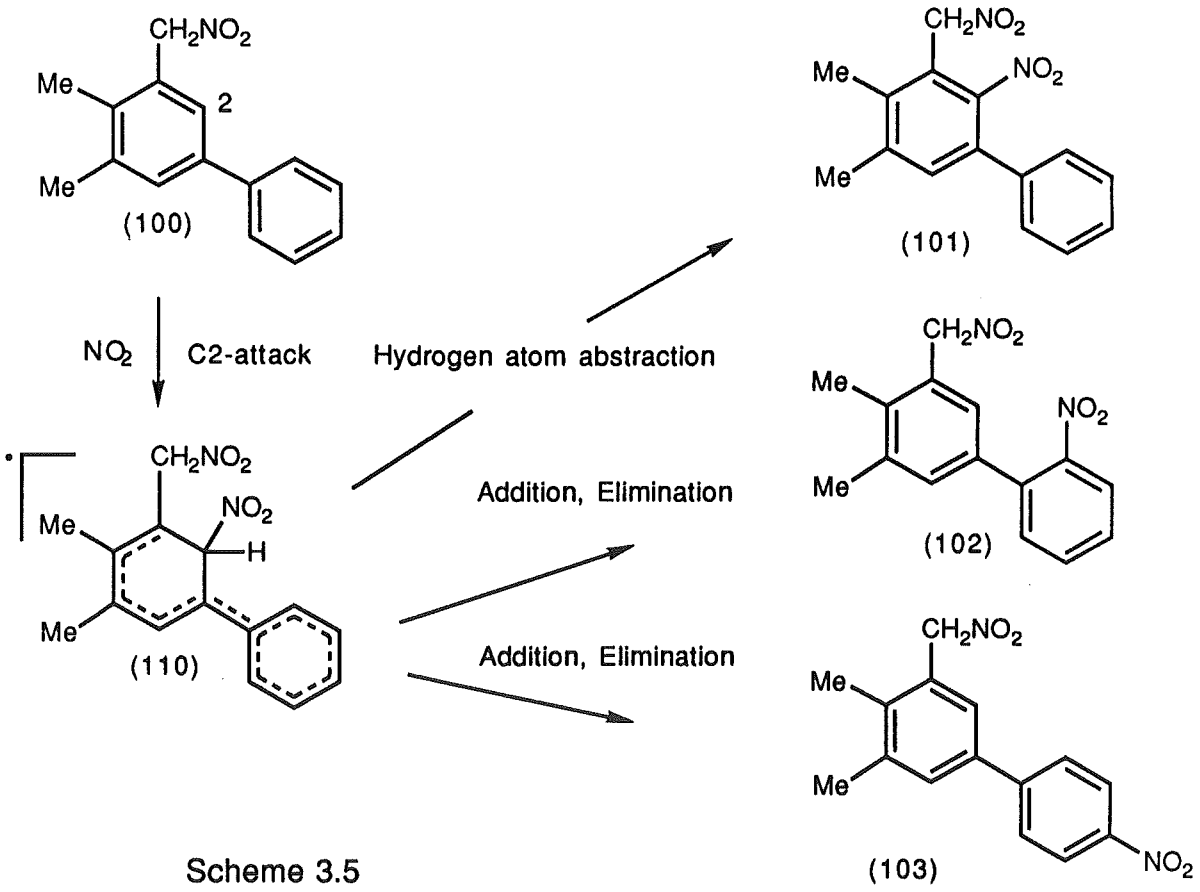
3.2.2 The Reaction of 4,5-Dimethyl-3-nitromethylbiphenyl (100) with Nitrogen Dioxide.

The reaction of 3-nitromethylbiphenyl (100) with nitrogen dioxide in benzene at < 5° gave a mixture shown (^{1}H n.m.r.) to be: 2-nitro-3-nitromethylbiphenyl (101) (23%), 2'-nitro-3-nitromethylbiphenyl (102) (38%) and 4'-nitro-3-nitromethyl-biphenyl (103) (38%). Within the accuracy of the ^{1}H n.m.r. spectroscopy the proportion of each isomer here is the same as that observed in the reaction of 3,4,5-trimethylbiphenyl (91) with nitrogen dioxide in benzene (Section 3.2.1).

That compounds (101), (102) and (103) are formed from 3-nitromethylbiphenyl (100) when 3,4,5-trimethylbiphenyl (91) was treated with nitrogen dioxide in Section 3.2.1 was shown by this result and it was supported by the low proportion of compounds (101), (102) and (103) found in Section 3.2.1. A likely mode of formation of the nitromethyl-nitrobiphenyl compounds (101), (102) and (103) is as shown in Scheme 3.5. This reaction pathway was also supported by resubmission experiments that showed that when the 2-, 2'- and 4'- nitro-biphenyls (97), (98) and (99) were treated with nitrogen dioxide at best only limited (6%) reaction was observed.

Reaction of the 3-nitromethylbiphenyl compound (100) with nitrogen dioxide would proceed by the mechanistic pathway shown in Scheme 3.5. Nitrogen dioxide attack[§] solely at the 2-position of 3-nitromethylbiphenyl compound (100), presumably because of electronic interactions between the nitro-group and the incoming nitrogen dioxide, would give the delocalised radical species (110). Subsequent hydrogen

abstraction similar to that shown in Scheme 3.2 would then give 2-nitro-3-nitromethylbiphenyl (101). Nitrogen dioxide coupling at the 2'-, 4'- and 6'- positions of (110) followed by elimination of nitrous acid would lead to 2'-nitro-3-nitromethylbiphenyl (102) and 4'-nitro-3-nitromethylbiphenyl (103). This reaction pathway is analogous to the reaction pathway shown in Scheme 3.3.



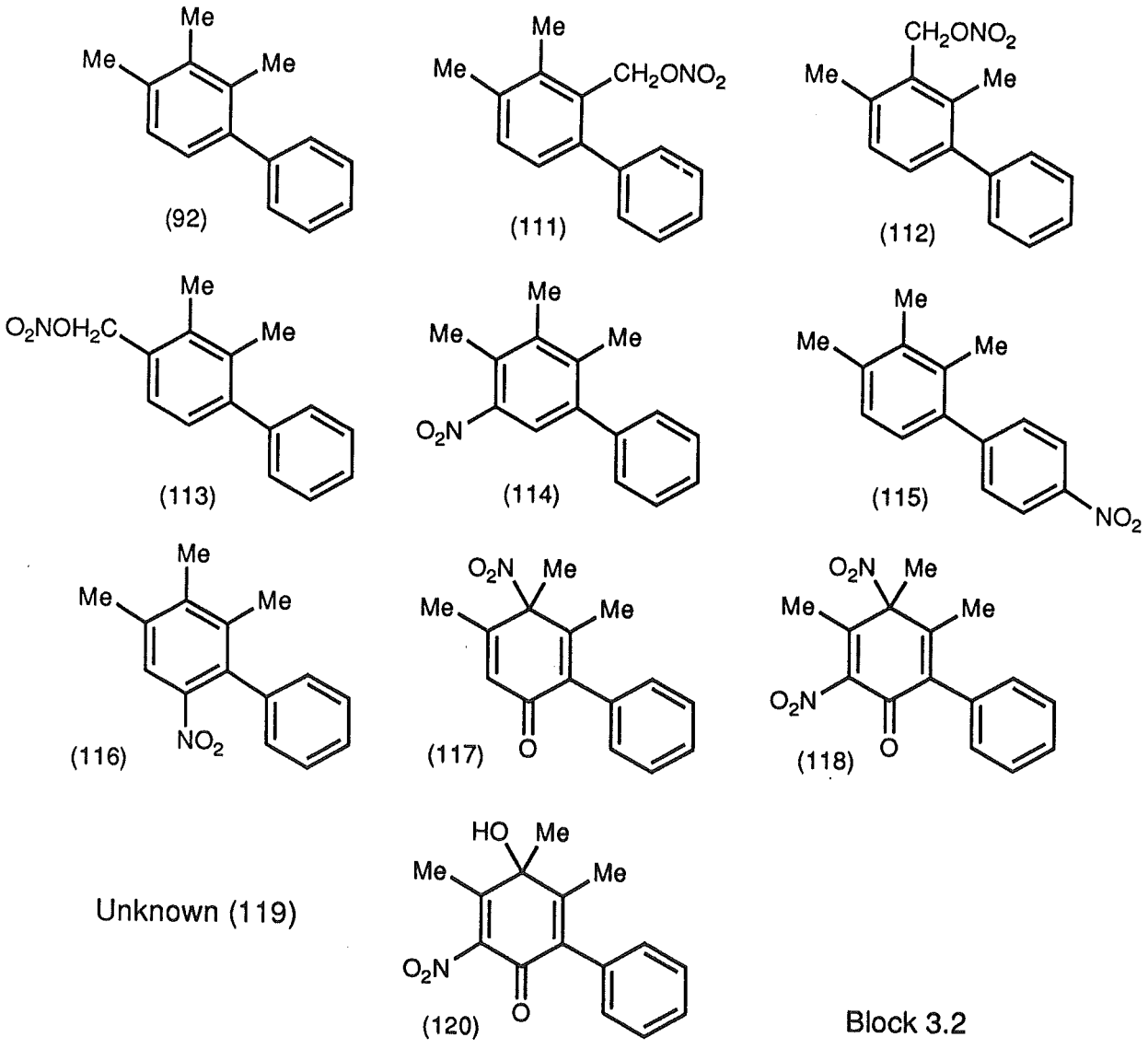
Scheme 3.5

3.3 The Reactions of 2,3,4-Trimethylbiphenyl (92) and Related Compounds with Nitrogen Dioxide.

3.3.1 The Reactions of 2,3,4-Trimethylbiphenyl (92) with Nitrogen Dioxide.

Treatment of 2,3,4-trimethylbiphenyl (92) with nitrogen dioxide gave a crude product shown (^{1}H n.m.r.) to be a mixture of: 3,4-dimethyl-2-nitratomethylbiphenyl (111) (4%), 2,4-dimethyl-3-nitratomethylbiphenyl (112) (4%), 2,3-dimethyl-4-nitratomethylbiphenyl (113) (trace), 2,3,4-trimethyl-5-nitrobiphenyl (114) (34%), 2,3,4-trimethyl-4'-nitrobiphenyl (115) (9%), 2,3,4-trimethyl-6-nitrobiphenyl (116)

(22%), 3,4,5-trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117) (9%), 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118) (9%), and unknown (119) (9%), see Block 3.2.



Block 3.2

This mixture was first separated into two fractions by normal phase HPLC using an Alltech CN 10 micron preparative HPLC column. The non-polar fraction was the fraction eluted by 20% dichloromethane in hexane and the polar fraction was the fraction eluted with dichloromethane. Chromatography of the non-polar fraction on a Chromatotron silica gel plate at room temperature gave, in order of elution:

3,4-Dimethyl-2-nitratomethylbiphenyl (111), an oil, was identified by:

(i) The mass spectrum [*c.* Found M^++1 (methane C.I.) = 258.1128. $C_{12}H_{16}NO_3$ requires 258.1130] that established a stoichiometry with a nitrate group.

(ii) The presence of a peak at (*c.* δ 5.54) for a X-substituted methyl group in the ^{1}H n.m.r. spectra and the presence in the infrared spectra of the substituent bands expected for the nitrate group (*c.* 1630, 1290, 860 cm^{-1}) led to the assignment of compound (111) as a nitratomethyl substituted biphenyl. The n.O.e. difference experiments placed this nitratomethyl group at the two position: Saturating the ^{1}H n.m.r. peak at δ 2.19 (4-methyl) gave positive n.O.e. difference peaks at δ 2.35 (3-methyl) and δ 7.25 (H5), and saturating the ^{1}H n.m.r. peak at δ 2.35 (3-methyl) gave positive n.O.e. difference peaks at δ 2.19 (4-methyl) and δ 5.54 (nitratomethyl) consistent with this assignment.

The second compound eluted, was only obtained in admixture with compound (113). It was assigned the 2,4-dimethyl-3-nitratomethylbiphenyl structure (112) because the infrared spectra contained the substituent bands (*c.* 1630, 1290, 860 cm^{-1}) of a nitrate group and because the ^{1}H n.m.r. spectra contained a peak at (*c.* δ 5.65) for a nitratomethyl group. The n.O.e. difference experiment where the δ 5.39 ^{1}H n.m.r. peak (nitratomethyl) was saturated gave two positive n.O.e. difference peaks at δ 2.28 (2-methyl) and δ 2.46 (4-methyl), thus the nitratomethyl group is at the 3-position.

The third compound in this series was assigned as 2,3-dimethyl-4-nitrato-methylbiphenyl (113) on the basis of:

(i) Mass spectroscopy [*c.* Found M^+ (methane C.I.) = 257.1061. $C_{12}H_{15}NO_3$ requires 257.1061] that established a stoichiometry with a nitrate group.

(ii) The presence of a peak (*c.* δ 5.39) in the ^{1}H n.m.r. spectra and the presence in the infrared spectra of the substituent bands expected for the nitrate group (*c.* 1630, 1280, 860 cm^{-1}). The nitratomethyl-substituent was placed at the 4-position by exclusion.

The fourth compound eluted was assigned the 2,3,4-trimethyl-5-nitrobiphenyl structure (114) on the basis of:

(i) The mass spectrum that established a stoichiometry with a single nitro-group [*c.* Found $M^+ + 1$ (isobutane C.I.) 242.1192 $C_{15}H_{16}NO_2$ requires 242.1181].

(ii) The presence in the infrared spectra of nitro-substituent bands (*c.* 1523, 1358 cm^{-1}).

(iii) The peak at (*c.* δ 7.52) in the ^{1}H n.m.r. spectra is a singlet pointing to substitution on ring one and the n.O.e. difference experiments (saturating the δ 7.52 peak due to the one-proton signal corresponding to the single aromatic proton on ring one failed to give a positive n.O.e. difference peak at δ 2.44 for the 4-methyl group) placed the nitro-substituent unambiguously at the 5-position.

The fifth compound eluted, 2,3,4-trimethyl-4'-nitrobiphenyl, m.p. 114-117°, was assigned structure (115) on the basis of:

(i) A mass spectrum [*c.* Found M^++1 (isobutane C.I.) 242.1192 $C_{15}H_{16}NO_2$ requires 242.1181] that established a stoichiometry with a single nitro-group.

(ii) The presence in the infrared spectra of nitro substituent bands (*c.* 1517, 1350 cm^{-1}) and the presence in the ^{1}H n.m.r. spectra of two AB quartets (*c.* δ 6.97, d ($J_{H6,H5}$ 7.9 Hz), H6; 7.10, d ($J_{H5,H6}$ 7.9 Hz), H5; 7.45, d ($J_{H2',H3';H6',H5'}$ 8.8 Hz), H2' H6'; 8.26, d ($J_{H3',H2';H5',H6'}$ 8.8 Hz), H3', H5') unambiguously located the nitro-group at the 4'-position.

The final compound eluted, 2,3,4-trimethyl-6-nitrobiphenyl (116), m.p. 109-110°, is a new compound. It was assigned on the basis of:

(i) An elemental analysis (*c.* Found C, 74.5; H, 6.2; N, 5.8 %. $C_{15}H_{15}NO_2$ required C, 74.7; H, 6.3; N, 5.8 %) that established a stoichiometry with a single nitro-group.

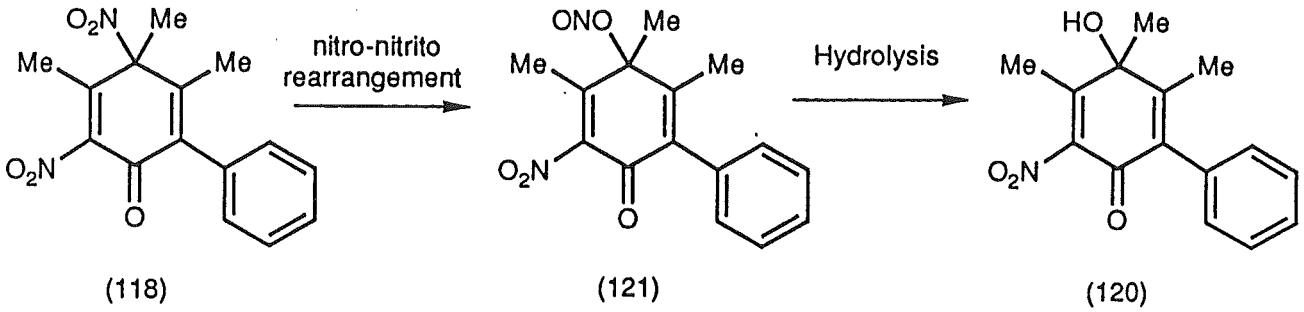
(ii) The infrared spectra contained nitro substituent bands (*c.* 1510, 1330 cm^{-1}).

(iii) The peak at (*c.* δ 7.53) in the ^{1}H n.m.r. spectra is a singlet pointing to substitution on ring one and the n.O.e. difference experiments [saturating the δ 7.53 peak assigned to H5 gave a positive n.O.e. difference peak at δ 2.40 (2%) for the 4-methyl group] placed the nitro-substituent unambiguously at the 6-position.

Separation of the more polar fraction from the HPLC, above, using a Chromatotron silica gel plate at low temperature gave impure samples of three compounds present in the original product mixture.

Storage of the second compound eluted, 3,4,5-trimethyl-2,4-dinitro-6-phenyl-cyclohexa-2,5-dienone (118) in (D)-chloroform at 24° for one week gave 4-hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120), by the rearrangement

shown in Scheme 3.6. A similar rearrangement was described in Scheme 2.9 for the trimethyltrinitrocyclohexa-2,5-dienone (59).



(118) (121) (120)

Scheme 3.6

The structure of compound (120) was determined by a single crystal X-ray structure analysis. A perspective diagram of 4-hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120), m.p. 197-199°, $C_{15}H_{14}NO_4$, is presented in Figure 3.2 and the corresponding atomic coordinates are given in Table A.2.

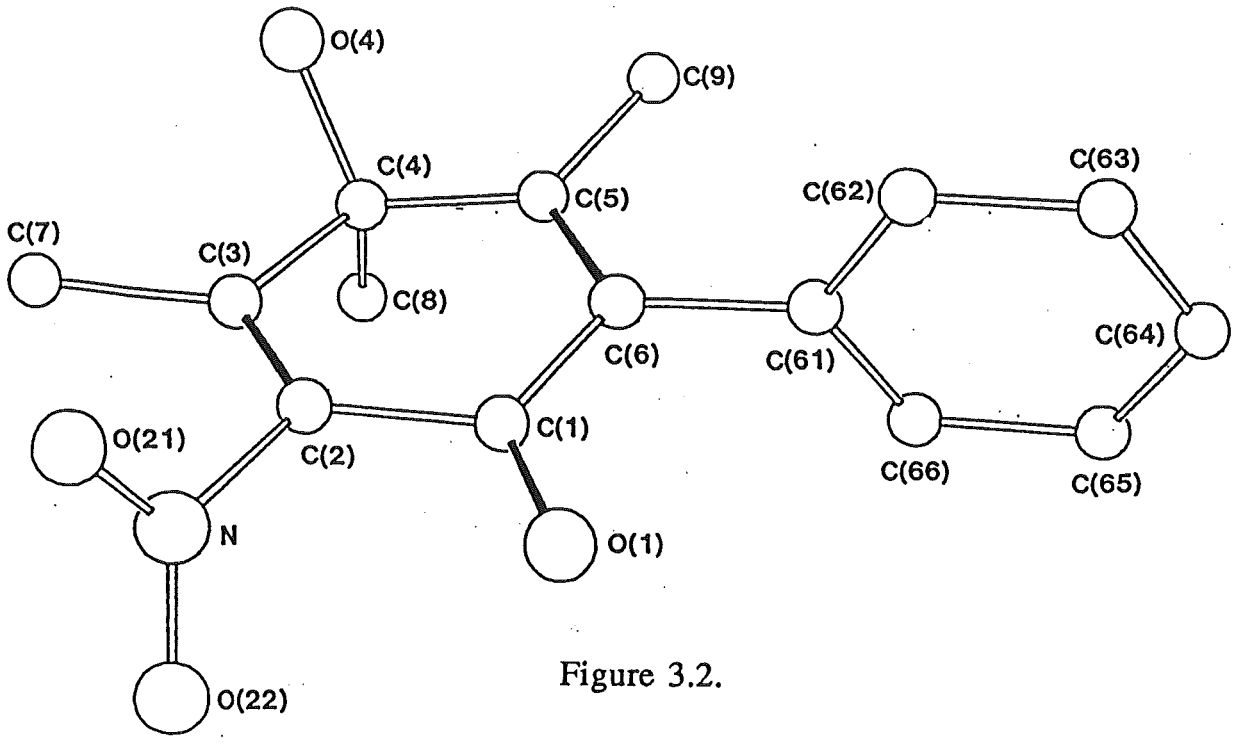


Figure 3.2.

In the solid state the alicyclic ring structure of compound (120) is distorted from planarity as shown by the torsion angle C(1)-C(2)-C(3)-C(4) 5.3°. This is reflected in the torsion angles C(7)-C(3)-C(4)-O(4) 41.3° and C(7)-C(3)-C(4)-C(8) -73.3° which would be equal if the alicyclic ring were planar. Both the nitro substituent and the phenyl group adopt conformations in the solid state at close to perpendicular to the plane of the alicyclic ring as shown by the torsion angles: O(21)-N-C(2)-C(1) 101.3° and C(5)-C(6)-C(61)-C(66) -88.5°. The packing diagram for compound (120) is shown in Figure 3.3, the distance between the hydrogen bonded O(4) and O(1) is 2.742 Å. The spectroscopic data for this compound are in accord with the 4-hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120) structure assigned above. Of particular interest is the infrared spectra which contained substituent bands expected for the hydroxy substituent (*c.* 3420 cm^{-1}), a free ketone (*c.* 1681 cm^{-1}), a hydrogen bonded ketone (*c.* 1640 cm^{-1}), and a nitro substituent (*c.* 1540, 1390, 738 cm^{-1}).

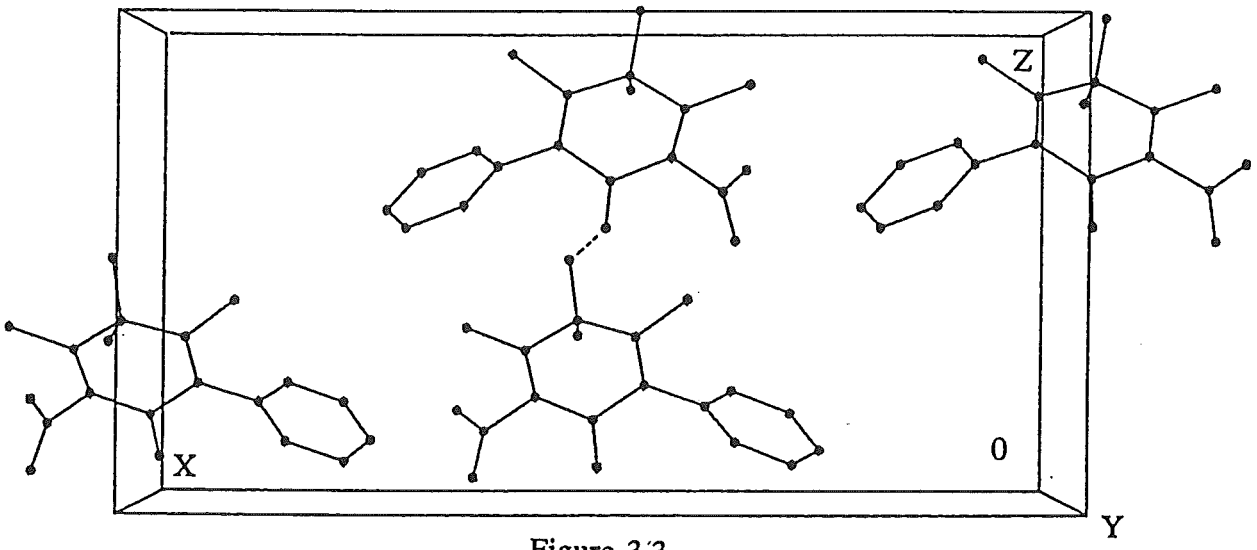


Figure 3.3.

The second compound eluted, was assigned the 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone structure (118) because it rearranged in (D)-chloroform to give 4-hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120). The presence of ketone (*c.* 1670 cm^{-1}) and nitro (*c.* 1550, 1380, 1359 cm^{-1}) substituent bands and the lack of a hydroxy substituent band in the infrared spectra of this parent compound

supports the structural assignment for compound (118) and is in keeping with the rearrangement shown in Scheme 3.6, above.

The first eluted compound was assigned as 3,4,5-trimethyl-4-nitro-2-phenyl-cyclohexa-2,5-dienone (117) on the basis of:

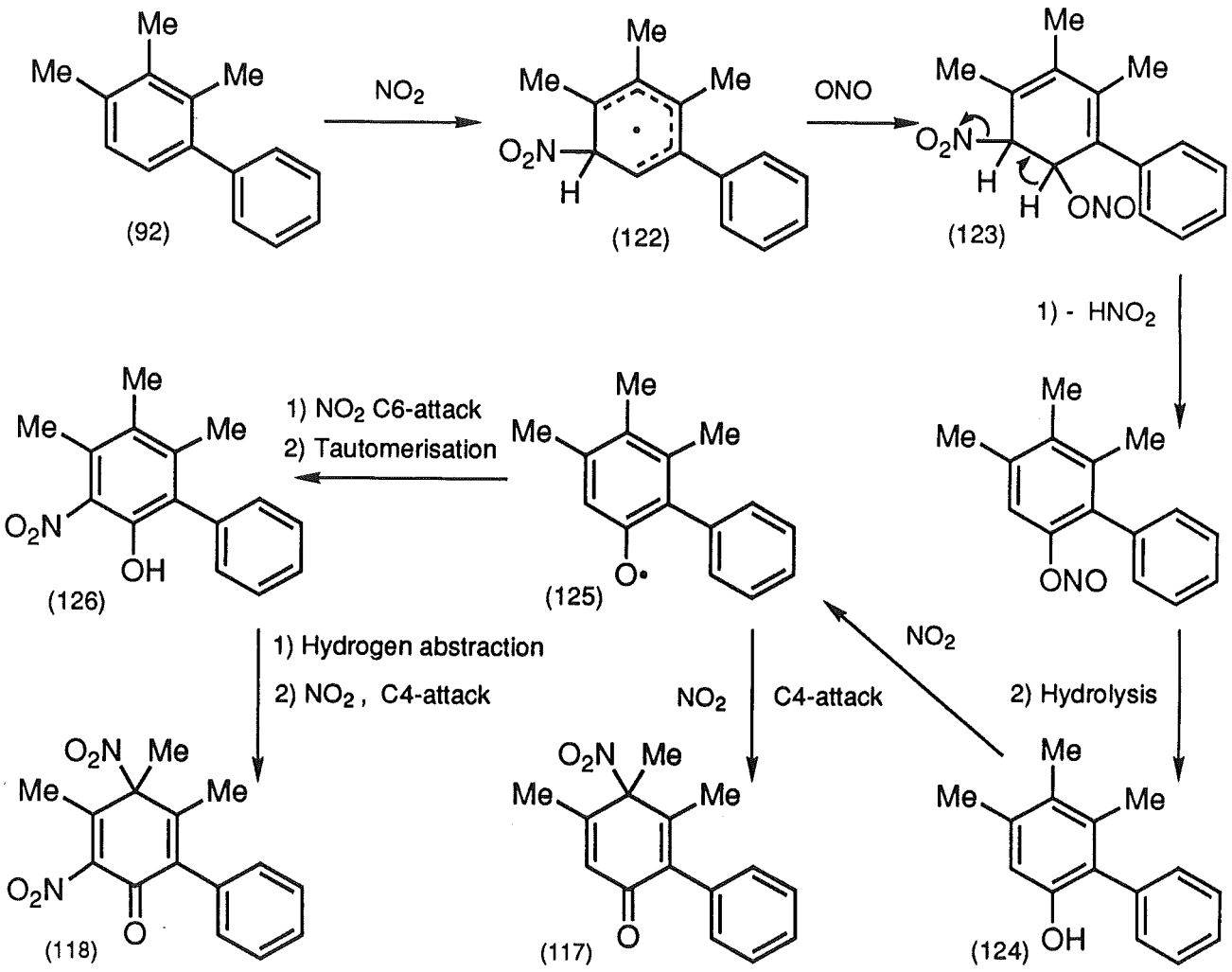
(i) The similarity of its physical behaviour on HPLC and thin layer chromatography to trimethyl-dinitrocyclohexa-2,5-dienone (120), identified above.

(ii) The infrared spectra that contained ketone (*c.* 1670 cm^{-1}) and nitro (*c.* 1550, 1380, 1350 cm^{-1}) but no hydroxy substituent bands.

(iii) The ^1H n.m.r. spectra [*c.* δ 1.81, s, Me; 1.97, s, Me; 2.03, d ($J_{4\text{-Me, H}}$ 1.5 Hz), 4-Me; 6.35, q ($J_{H,4\text{-Me}}$ 1.5 Hz), H; 7.13, m, two aromatic hydrogens; 7.42, m, three aromatic hydrogens] is similar to that of trimethyl-dinitrocyclohexa-2,5-dienone (120) but it contains the extra structural feature of a vinylic hydrogen coupled to a methyl substituent [*c.* δ 2.03, d ($J_{4\text{-Me,H}}$ 1.5 Hz), 4-Me; 6.35, q ($J_{H,4\text{-Me}}$ 1.5 Hz), H].

The final compound eluted, unknown (119), could not be identified.

3,4,5-Trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117) and 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone structure (118) are thought to be formed *via* the reaction pathway shown in Scheme 3.7.



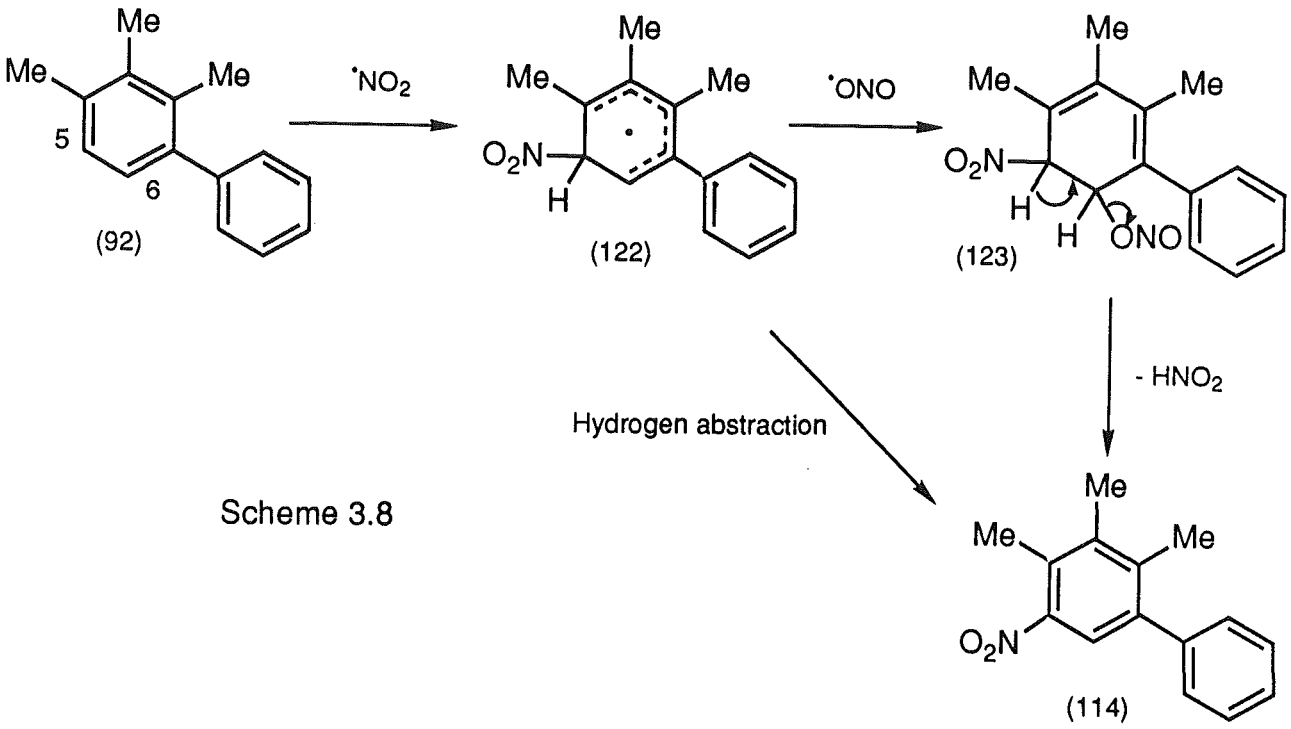
Scheme 3.7

In this reaction pathway nitrogen dioxide attacks the unsubstituted 5-position of biphenyl (92) to give the delocalised radical species (122); it is unlikely that there is significant delocalisation into ring two of this biphenyl because of steric interactions between the 2-methyl and the phenyl group. Coupling of a second molecule of nitrogen dioxide at C6 would then give intermediate (123). Addition reactions of this type are described in the literature.[103] The intermediate (123), formed by attack by two molecules of nitrogen dioxide on 2,3,4-trimethylbiphenyl (92), would give the phenol (124) after loss of the elements HNO_2 and hydrolysis. This phenol (124) would then become a substrate for further nitrogen dioxide attack following reaction pathways such as those described in Chapter 2 of this thesis. Specifically, after initial hydrogen abstraction by nitrogen dioxide to give the phenoxy radical (125) coupling with nitrogen dioxide at C4 would give

3,4,5-trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117) and coupling at the 6-position would give the keto tautomer of the nitrophenol (126). This phenol (126) could then react with further nitrogen dioxide to give 3,4,5-trimethyl-2,4-dinitro-6-phenyl-cyclohexa-2,5-dienone (118).

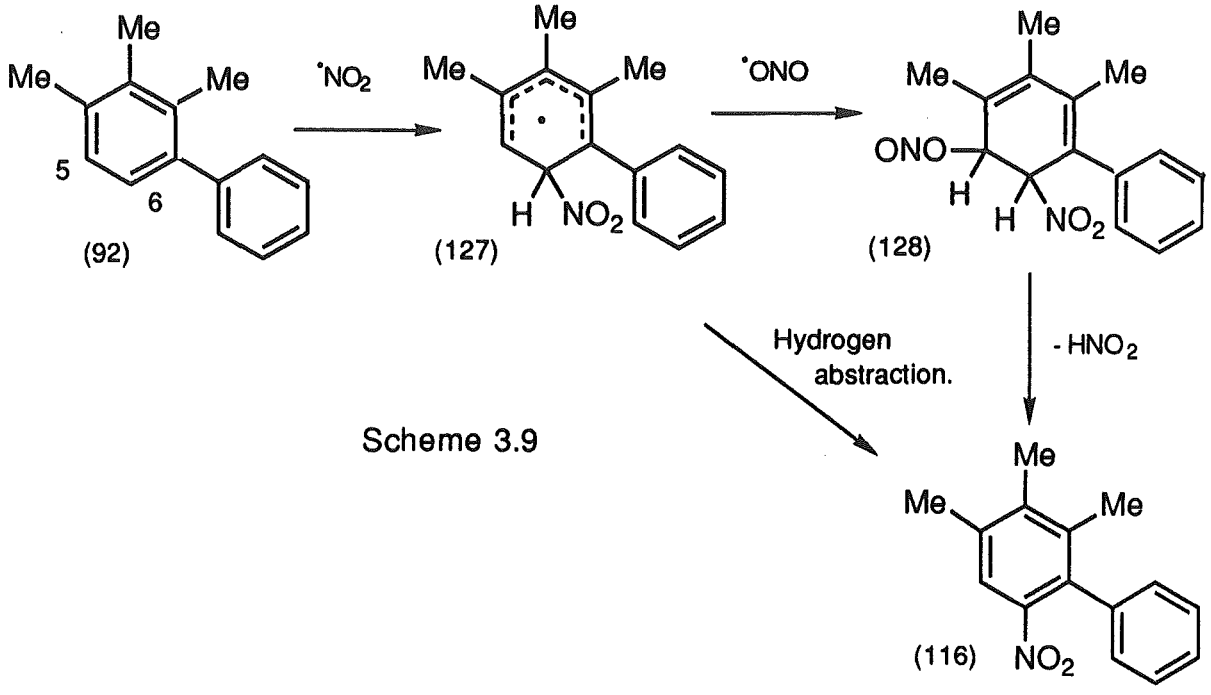
The formation of the two mononitrated compounds 2,3,4-trimethyl-5-nitrobiphenyl (114) and 2,3,4-trimethyl-6-nitrobiphenyl (116) in the reaction of 2,3,4-trimethylbiphenyl (92) are seen as occurring by a mechanism distinctly different from that proposed for the formation of the 2-nitrobiphenyl compound (97) in the reaction of 3,4,5-trimethylbiphenyl (91) in Section 3.2.1. This is because the adjacent unsubstituted ring positions on 2,3,4-trimethylbiphenyl (92) open the possibility of a different addition-elimination reaction pathway, Scheme 3.8. In this reaction pathway nitrogen dioxide attacks the unsubstituted 5-position of biphenyl (92) to give the delocalised radical species (122). Coupling of a second molecule of nitrogen dioxide at C6 would then give intermediate (123). Subsequent loss of nitrous acid would then give 5-nitrobiphenyl (114).

The alternative addition hydrogen abstraction mechanism for aromatic nitration that was described in Section 3.2.1 cannot be completely discounted in the formation of the 5-nitrobiphenyl (114) because it would be in competition with the addition-elimination reaction, described above, and because it would give the same product (114). See Scheme 3.8.



Scheme 3.8

2,3,4-Trimethyl-6-nitrobiphenyl (116) could be regarded as arising *via* the reaction pathway shown in Scheme 3.9. This is analogous to that described, above, for 2,3,4-trimethyl-5-nitrobiphenyl (114).



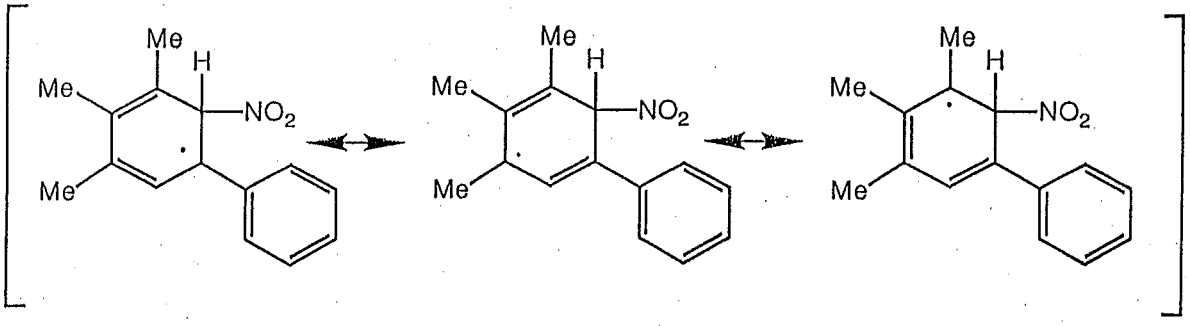
Scheme 3.9

3.4 Comparison between the Reaction of 3,4,5-Trimethybiphenyl (91) and 2,3,4-Trimethylbiphenyl (92) with Nitrogen Dioxide.

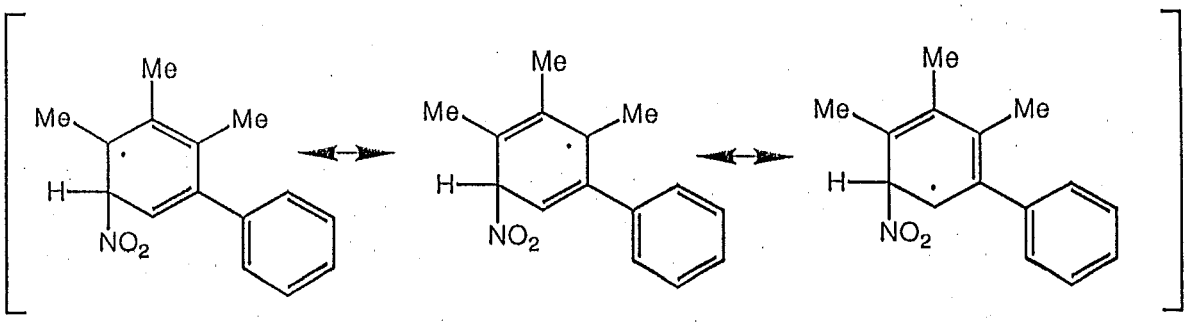
Two major differences are observed when the products of the two biphenyls (91) and (92) are compared.

(i) Treatment of 2,3,4-trimethylbiphenyl (92) with nitrogen dioxide gave cyclohexa-2,5-dienones (117) and (118) whereas 3,4,5-trimethylbiphenyl (91) did not give analogous compounds. The reason for this observation is that the delocalised radical species (104) formed by nitrogen dioxide attack at C2 on 3,4,5-trimethylbiphenyl (91) is substituted at both the adjacent positions (C1 and C3 on the biphenyl) so intermediates such as (123) and (128) are not formed.

(ii) 3,4,5-Trimethylbiphenyl (91) gave only one 5-nitromethylbiphenyl (100) whereas 2,3,4-trimethylbiphenyl (92) gave three nitratomethylbiphenyls, (111) (112) and (113), *i.e.* there is a change in the regioselectivity and in the type of product formed. The change in the regioselectivity is a consequence of the formation of two delocalised radical species (122) and (127) as the result of nitrogen dioxide attack on 2,3,4-trimethylbiphenyl (92) compared with the formation of only one possible delocalised radical species (104) in the case of 3,4,5-trimethylbiphenyl (91). The canonical forms of these delocalised radicals are shown below. If a methyl group is at a ring position having unpaired electron spin density, on one of these canonical forms, it will be transformed into a benzylic radical at that position, by the mechanism shown in Scheme 3.4. This leads to *either* a nitromethyl *or* a nitratomethyl group at that point. It is not clear why nitromethyl substituents are formed from 3,4,5-trimethylbiphenyl (91) while nitratomethyl substituents are the products of similar reaction of 2,3,4-trimethylbiphenyl (92).


Me
H
Me
NO2
Me
Me
H
Me
NO2
Me
Me
H
Me
NO2
Me

(104)


Me
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NO2
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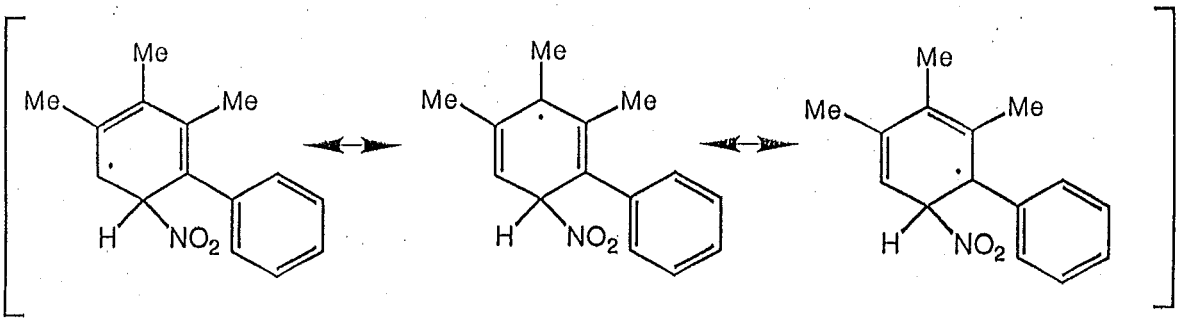
H
NO2

(122)


Me
Me
Me
H
NO2
Me
Me
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H
NO2
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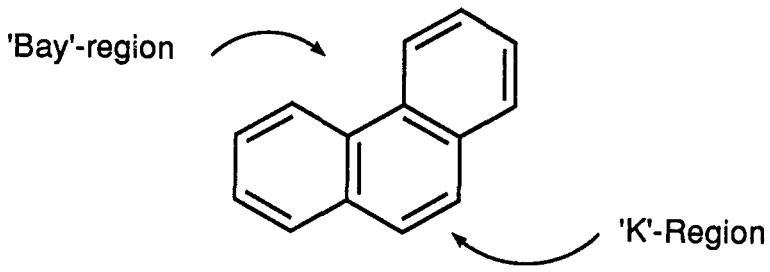
H
NO2

(127)

Chapter 4
The Reactions of Phenanthrene (130) with Nitrogen Dioxide.

4.1 Introduction.

In this Chapter are reported the results of the nitration reactions of phenanthrene (130) under free radical reaction conditions, *i.e.* with nitrogen dioxide in the non-polar solvent benzene. This study is of particular interest to environmental chemists as phenanthrene (130) and its nitro derivatives are ubiquitous anthropogenic compounds that are known mutagens.[104, 61] In addition to this phenanthrene, is the simplest PAH with the K-structural feature opposed to a "bay" region. The high double bond character of a K-region bond on a PAH exhibits properties which are similar to that of an isolated double bond; in particular, the K-region is susceptible to electrophilic and free radical attack.[105]



Nitration of phenanthrene under electrophilic conditions has been studied by Schmidt ,[106] by Dewar [107, 108] and by Svendesen.[109] These authors report the formation of mononitrophenanthrenes, with the major product being 9-nitrophenanthrene (131). Other researchers have reported the formation of adducts that are the result of addition reactions. The earliest example of this is the report by Schmidt[110] of the isolation of two addition products formulated as di-(9,10-dihydro-10-nitro-9-phenanthryl) ether and 9,9',10,10'-tetrahydro-10,10'-dinitro-9,9'-biphenanthryl. Grey and Baven[111] then showed that the 'ether' contained nitro and nitrate groups and they proposed the 10-nitro-10'-nitrato-9,9',10,10'-tetrahydro-9,9'-biphenanthryl structure (132). Subsequently, the stereochemistry of compound (132) was determined by ^{1}H n.m.r. spectroscopy.[112]

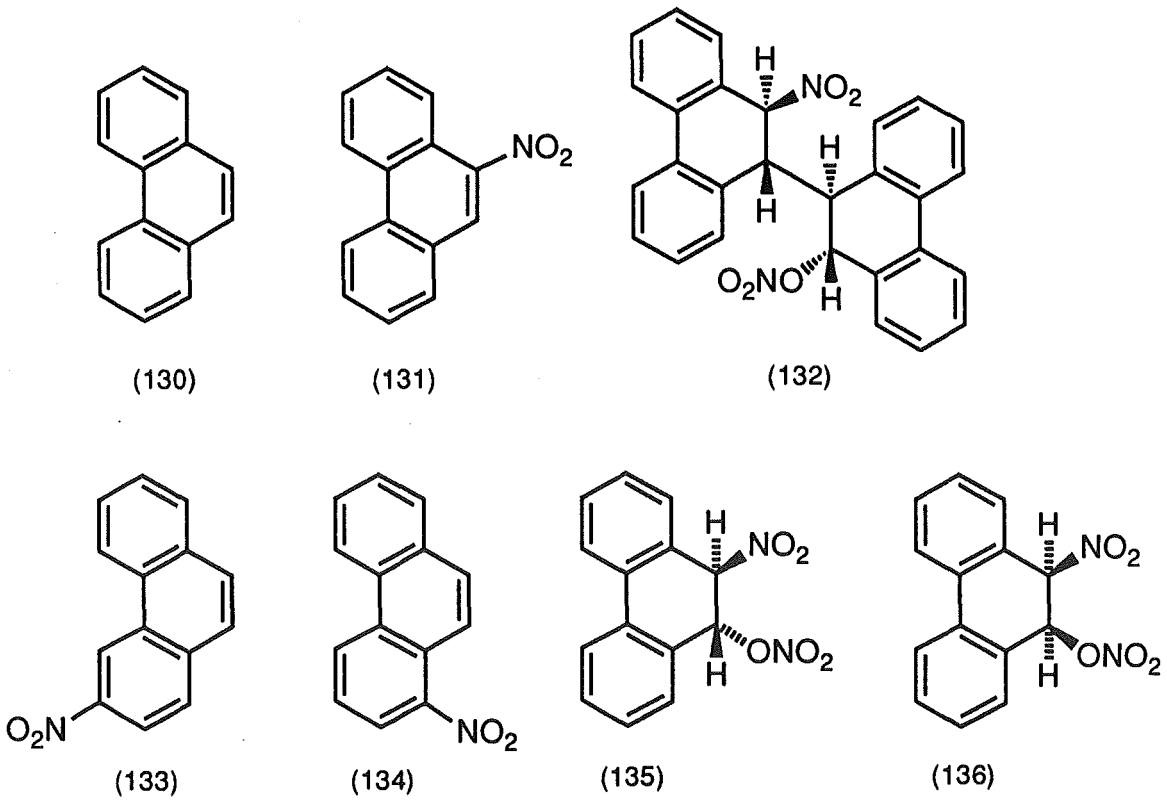
The reaction of phenanthrene with nitrogen dioxide under free radical conditions is reported to give a mixture of at least four mononitrated products[113] that were not further characterized, it is reported to be 'unclean',[63] and it is reported to give the dimeric

nitro,nitrate (132) in addition to the nitrophenanthrenes reported above.[114] In view of these contradictory reports and within the context of this thesis *i.e.* our interest in the free radical reactions of nitrogen dioxide with aromatic substrates, especially those of environmental interest, the reaction of phenanthrene (130) with nitrogen dioxide in benzene solution was re-examined.

4.2 The Reactions of Phenanthrene (130) with Nitrogen Dioxide in Benzene.

4.2.1 The Reaction of Phenanthrene (130) with Nitrogen Dioxide in Benzene.

Treatment of a solution of phenanthrene (130) in benzene (5.6×10^{-1} mole l^{-1}) with nitrogen dioxide in benzene for two hours gave a mixture (^1H n.m.r.) of dimeric nitro nitrate (132) (12%), 9-nitrophenanthrene (131) (37%), 3-nitrophenanthrene (133) (8%), 1-nitrophenanthrene (134) (9%), *trans* -nitro nitrate (135) (26%) and *cis* -nitro nitrate (136) (8%). See Block 4.1.



(130) (131) (132) (133) (134) (135) (136)

Block 4.1

Filtration of the reaction mixture after removal of excess nitrogen dioxide gave: 10'-nitro-9,9',10,10'-tetrahydro-9,9'-biphenanthren-10-yl nitrate (132), m.p. 153-154° (Lit.[114] 156-158°). This compound was identified on the basis of the spectral data:

(i) The infrared spectra contains both nitrate (*c.* 1620, 1251, 732 cm^{-1}) and nitro (*c.* 1550, 1335 cm^{-1}) substituent bands.

(ii) The ^1H n.m.r. spectra and the n.O.e. results are in accord with the stereochemistry assigned by Cohen *et. al.*,[112] Figure 4.1. In the dimeric nitro nitrate (132) H9 and H9' are *trans* to each other and they are *gauche* to H10 and H10', respectively, as shown by the proton-proton coupling constants. Further, the n.O.e. results are consistent with the assigned stereochemistry. Irradiation of H10' (δ 5.76) geminal to the nitro group gave positive n.O.e. difference peaks at H9' (δ 2.98) and H8 (δ 6.96), and irradiation of H10 (δ 5.25) resulted in positive n.O.e. difference peaks at H9 (δ 3.51) and H8' (δ 6.87). These observations are consistent with the close proximity in structure (132) (Fig. 4.1) of H10 to H9 and H8', and H10' to H9' and H8.

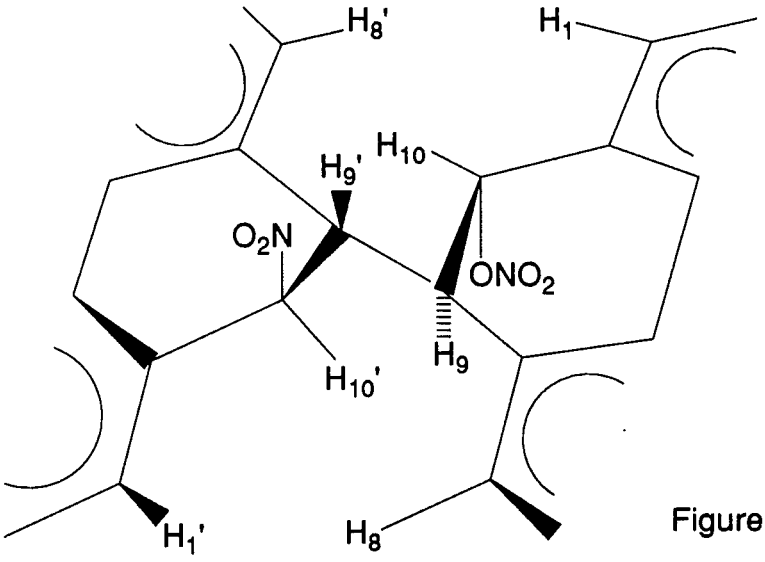
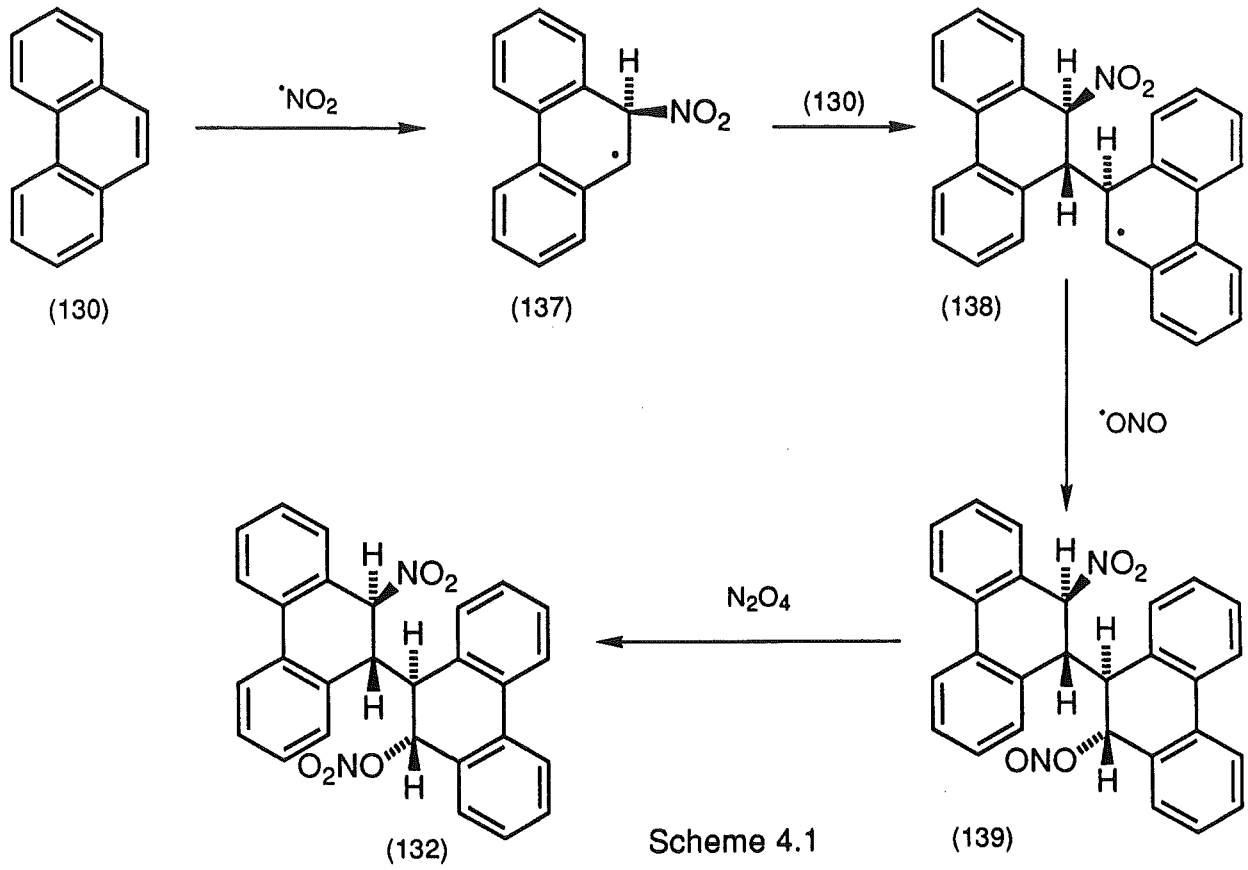


Figure 4.1

The dimeric nitro nitrate (132) is thought to be the product of the reaction pathway shown in Scheme 4.1. In this reaction the delocalised free radical (137) formed by nitrogen centred nitrogen dioxide attack at C9 on the phenanthrene molecule (130) itself undergoes reaction with another phenanthrene molecule (130) to give a second radical species (138). This radical (138) is then the subject of further nitrogen dioxide attack to give the dimeric nitro nitrite (139). Oxidation would then give the isolated dimeric nitro nitrate (132).[115]



Scheme 4.1

Chromatography of the residue, after removal of the dimeric nitro nitrate (132), on a Chromatotron silica gel plate gave three compounds, in order of elution:

9-Nitrophenanthrene (131) m.p. 114-115° (Lit.[86] 116-117°) was identified by the spectroscopic data, in particular:

(i) The infrared spectra revealed nitro substituent bands (*c.* 1511, 1450 cm^{-1}).

(ii) By comparison of the ^1H n.m.r. spectra of compound (131) to the reported ^1H n.m.r. spectra of 9-nitrophenanthrene.[116] 9-Nitrophenanthrene (131) is the only nitrophenanthrene isomer with a singlet assigned to H10 (*c.* δ 8.42) and a doublet due to H8 (*c.* 8.65) with an 8.1 Hz coupling constant.

The second compound eluted, 3-nitrophenanthrene (133) m.p.175.5-176° (Lit.[86] 170-171°), was identified by:

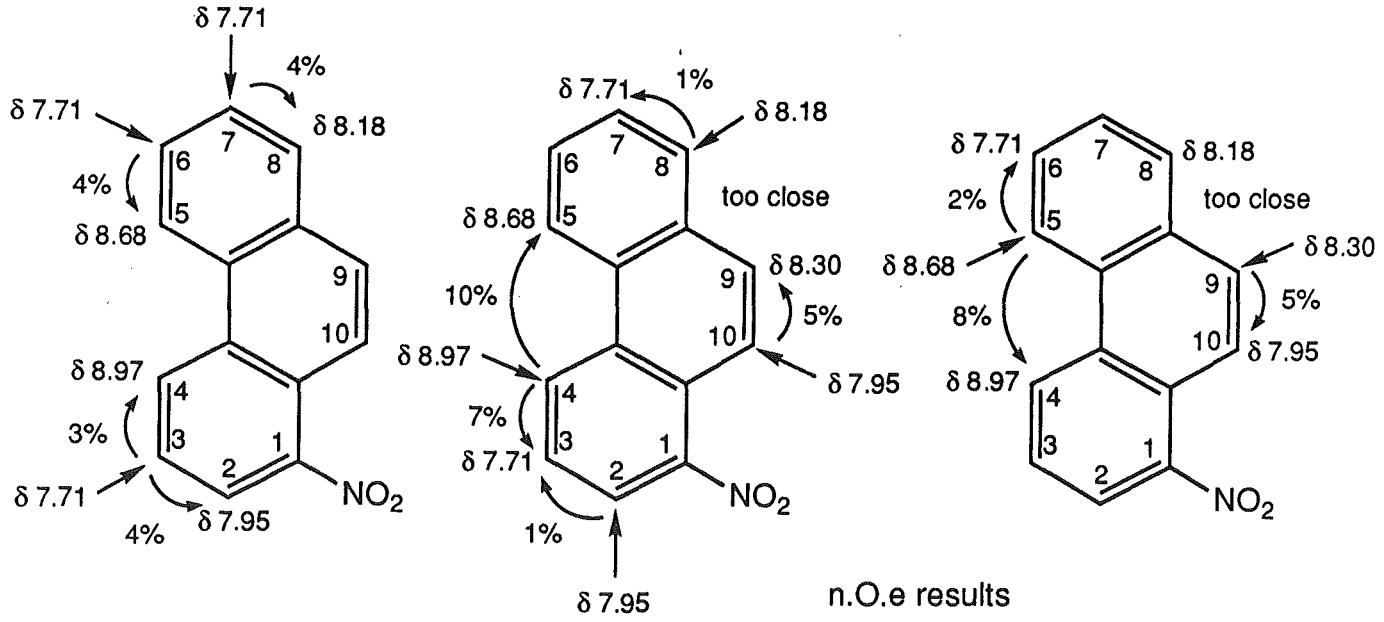
(i) The infrared spectra with nitro substituent bands (*c.* 1603, 1335 cm^{-1}).

(ii) 3-Nitrophenanthrene is the only nitrophenanthrene isomer with a ^{1}H n.m.r. peak, assigned to H4, at δ 9.62.[116] This resonance is a doublet with a 2.3 Hz coupling constant to H2.

The final compound eluted, 1-nitrophenanthrene (134) m.p. 131-132° (Lit.[117] 133-134°) was assigned on the basis of the spectroscopic data:

(i) The infrared spectra that exhibited nitro substituent bands (*c.* 1520, 1340 cm^{-1}).

(ii) The ^{1}H n.m.r. and the n.O.e. difference experiments support this assignment. These data are presented in Figure 4.2.



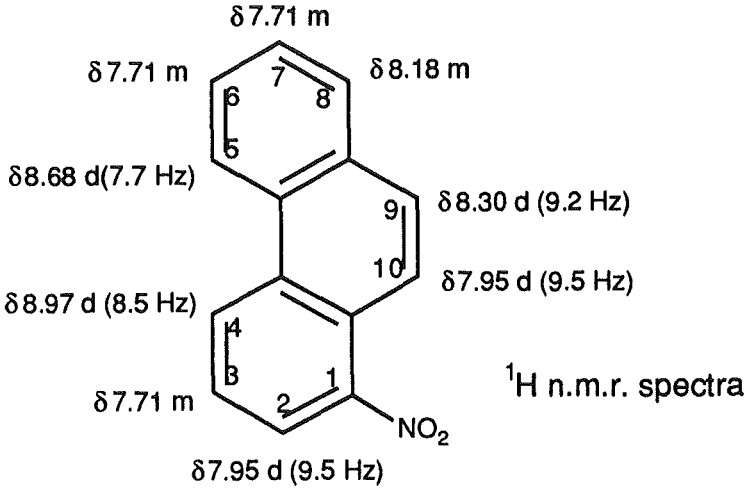
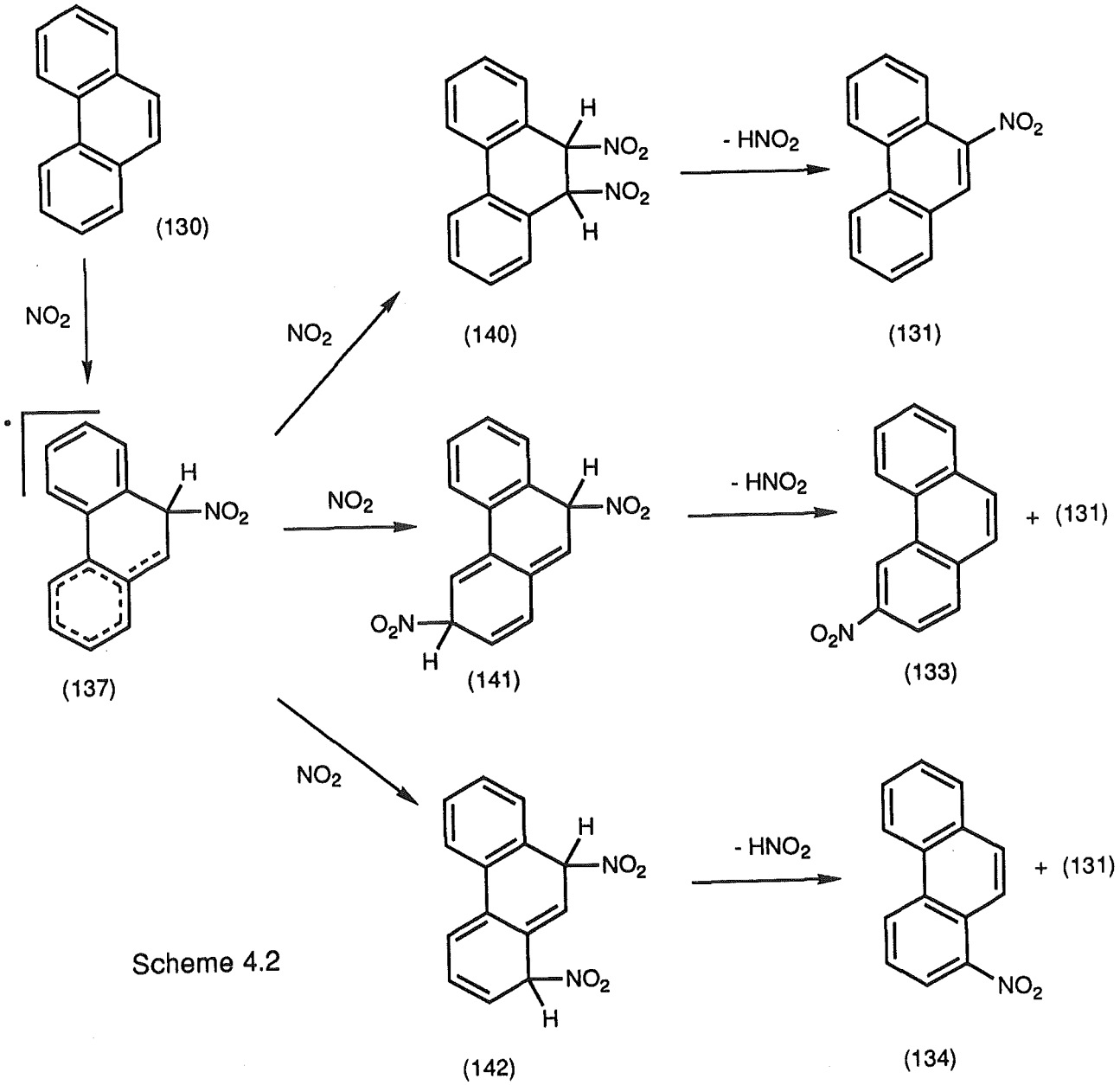


Figure 4.2

That there are no isolated singlets, such as H10 of 9-nitrophenanthrene (131) or H4 of 3-nitrophenanthrene (133), places the nitro substituent at the 1- or the 4- position. However the ^1H n.m.r. spectra of (134) contains two low field peaks (*c.* δ 8.68, 8.97) assigned by position and coupling constant to H5 and H4. This rules out substitution at the 4-position and the compound is therefore assigned the 1-nitrophenanthrene (134) structure.

The mononitrated phenanthrenes (131), (133) and (134) are thought to be formed as the result of the addition elimination pathway shown in Scheme 4.2.



Scheme 4.2

Nitrogen dioxide attack at the 9-position of the phenanthrene molecule with C-N bond formation would give the delocalised radical species (137). This unpaired electron species (unpaired electron spin density on C10, C1 and C3) would then be the subject of further nitrogen dioxide attack to give the dinitro compounds (140), (141) and (142). Subsequent loss of nitrous acid would then give nitrated phenanthrenes (131), (133) and (134). This reaction mechanism explains the surprising lack of 2- and 4- nitrophenanthrenes from the reaction products because little unpaired electron spin density is found at these positions.

The nitro nitrates (135) and (136) decomposed on a Chromatotron silica gel plate and these compounds were isolated by H.P.L.C.

A single crystal X-ray structure analysis of the first compound eluted (135) was carried out. A perspective drawing of *trans*-10-nitro-9,10-dihydro-phenanthren-9-yl nitrate (135), $C_{14}H_{10}N_2O_5$, m.p. 95-96°, is presented in Figure 4.3 with the

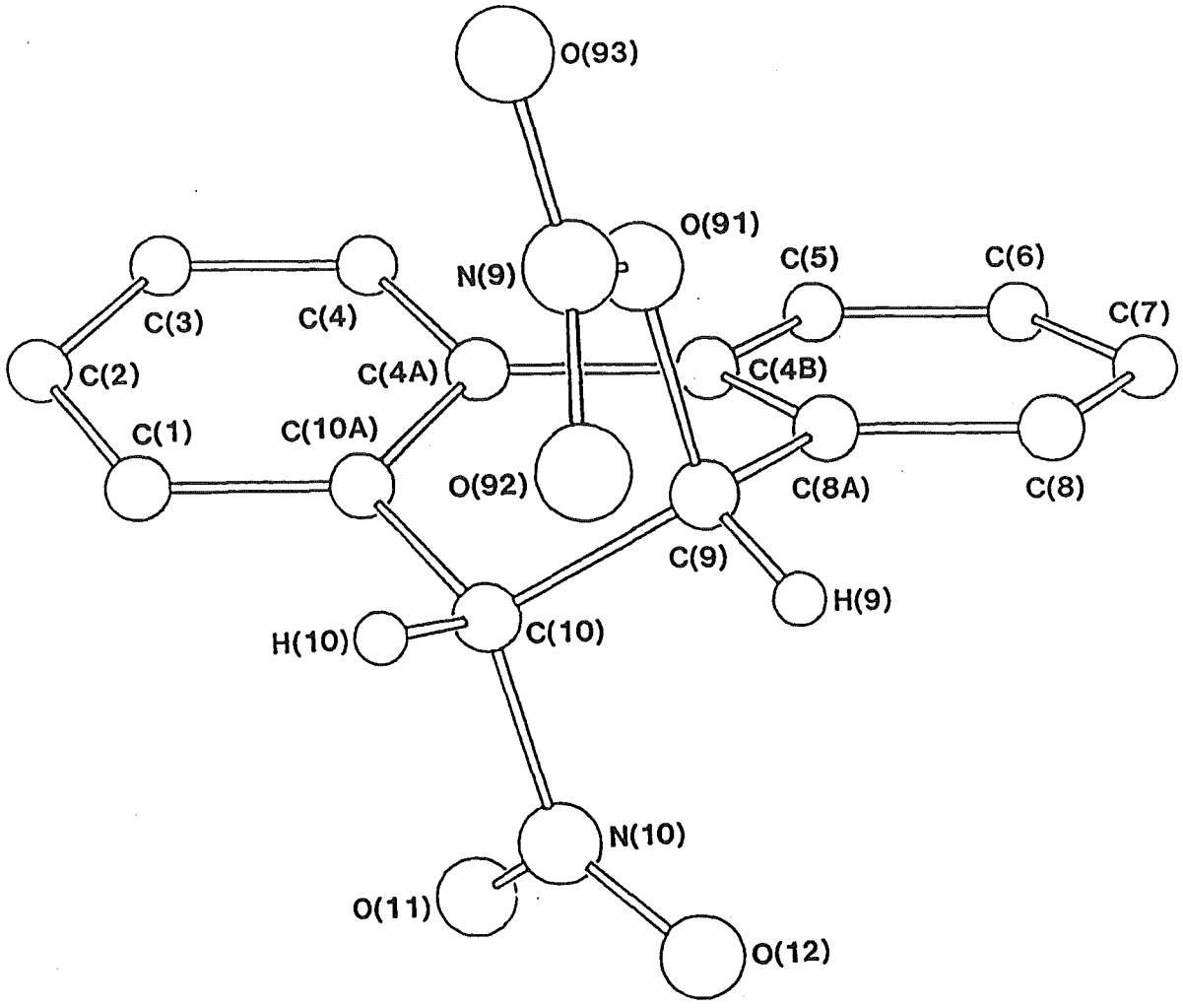
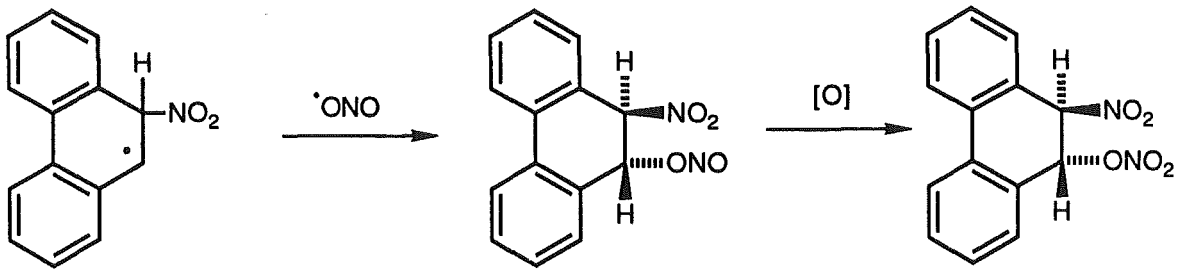


Figure 4.3.

In the solid state the two phenyl rings are displaced from coplanarity [torsion angle: C(8A)-C(4B)-C(4A)-C(10A) -17.8°] and the nitro and nitrato groups are close to *anti* to each other [torsion angle: N(10)-C(10)-C(9)-O(91) -175.8°]. The orientation of the nitrato group is shown by the torsion angles H(9)-C(9)-O(91)-N(9) -39.6°, C(9)-O(91)-N(9)-O(92) 1.2°, and the plane of the nitro group is close to being eclipsed with the C(10)-C(10A) bond [torsion angle: C(10A)-C(10)-N(10)-O(11) -15.7°. The spectroscopic data for the *trans* -nitro nitrate (135) were consistent with the established structure. In particular, the infrared spectra contains nitrato (*c.* 1618, 1254, 835 cm^{-1}) and nitro (*c.* 1546, 1345 cm^{-1}) substituent bands, and the ^1H n.m.r. spectra contains two doublets [*c.* 5.84, d ($J_{H10,H9}$ 3.4 Hz), H10; 6.73, d ($J_{H9,H10}$ 3.4 Hz), H9] with the position and proton-proton coupling constants in accord with the H(9)-C(9)-C(10)-H(10) torsional angle (69.6°).[83] The n.O.e. experiments also placed the H9 and H10 in *equatorial* positions: irradiation of H9 (*c.* δ 6.73) gave positive difference peaks for H8 (*c.* 7.53) and H10 (*c.* 5.84) and irradiation of H10 (*c.* 5.84) gave positive difference peaks for H1 (*c.* 7.46) and H9 (*c.* 6.73).

The *trans* -nitro nitrate (135) could be formed by the pathway shown in Scheme 4.3. The delocalised free radical (137) formed as the result of nitrogen centred nitrogen dioxide attack at the 9-position of phenanthrene (130) would couple with the nitrogen centre of nitrogen dioxide to give the nitro nitrite compounds (143). Subsequent oxidation would then give the isolated compound (135).[115]



(137) (143) (135)

Scheme 4.3

The second compound eluted was obtained only in admixture with the *trans* -isomer (135). It was assigned the *cis* -10-nitro-9,10-dihydrophenanthren-9-yl nitrate structure (136) (Figure 4.4) on the basis of the spectroscopic data:

(i) The presence in the infrared spectra of the mixture of a second set of bands corresponding to the nitrato (*c.* 1658, 1288, 840 cm^{-1}) and nitro (*c.* 1520, 1368 cm^{-1}) substituents.

(ii) The similarity of its ^1H n.m.r. spectra to that of the *trans* -isomer (135). The ^1H n.m.r. spectra contains two doublets assigned to H9 and H10 [*c.* δ 5.98, d, ($J_{H10,H9}$ 4.8 Hz), H10; 6.58, d ($J_{H9,H10}$ 4.8 Hz), H9] consistent with the *cis-axial-equatorial* stereochemistry. More importantly, the n.O.e. results are consistent with the proposed stereochemistry. Irradiation of the H9 proton (δ 6.58) gave only one positive n.O.e. difference peak at δ 5.98 (H10), and irradiation of the H10 proton (δ 5.98) gave two positive n.O.e. difference peaks at δ 6.58 (H9) and δ 7.49 (H1). These observations are in keeping with the close proximity in structure (136) of H9 to H10, and of H10 to H9 and H1.

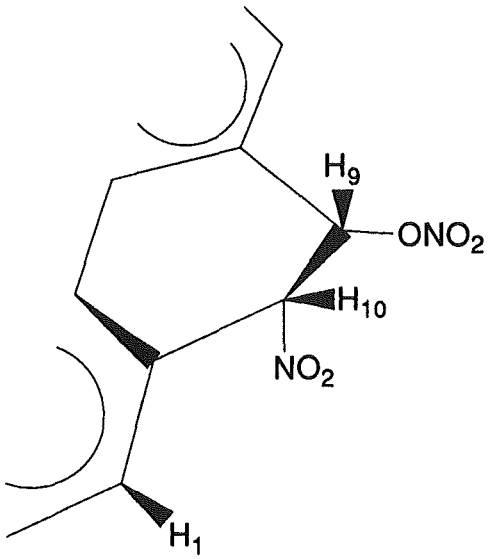


Figure 4.4

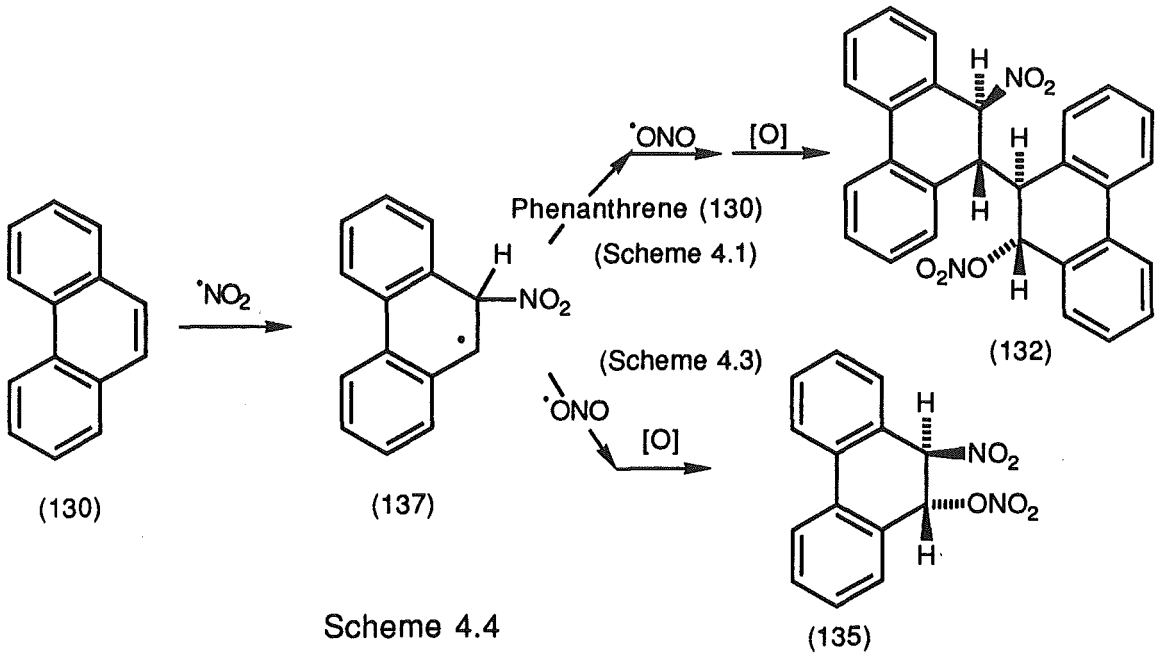
Given the presence of both monomeric and dimeric nitro nitrates among the products of this reaction, the effect of changing the phenanthrene concentration on the

course of the reaction with nitrogen dioxide was explored: the results of these experiments are given in Table 4.1.

Table 4.1. Variation of Product Yields with Phenanthrene (130) Concentration.

Phenanthrene	Product Yields (%)					
Concentration	(132)	(135)	(136)	(131)	(133)	(134)
1.4 M	20	22	9	29	8	13
5.6×10^{-1} M	12	26	8	37	8	9
5.6×10^{-2} M	trace	42	8	23	11	15

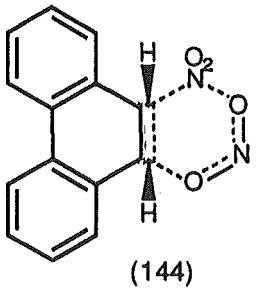
The overall yield of nitrophenanthrenes formed remains approximately 50% regardless of the phenanthrene concentration. The remaining compounds, all of which have the nitro nitrate structural feature, make up the remaining 50% of the products. The yields of two of the compounds with the nitro nitrate structural feature (132) and (135) change markedly with the phenanthrene (130) concentration.



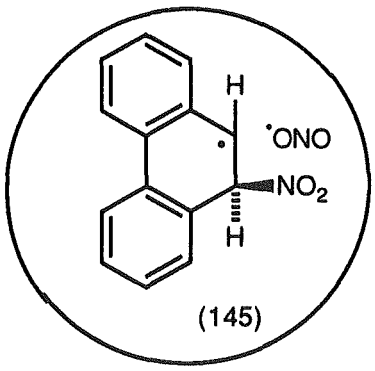
Scheme 4.4

The variation in the yields of the dimeric nitro nitrate (132) and the *trans* -nitro nitrate (135) with the phenanthrene concentration is consistent with competition between $^{\bullet}NO_2$ and phenanthrene (130) for reaction with the nitrophenanthryl radical (137) with the attack occurring in both cases *trans* to the nitro-group. Scheme 4.4.

Although this accounts for the variation in the yields of the dimeric nitro nitrate (132) and the *trans* -nitro nitrate (135) with the phenanthrene (130) concentration, it does not explain the invariant yield of *cis* -nitro nitrate (136). It is thought possible that the *cis* -nitro nitrate (136) is the product of dinitrogen tetraoxide addition to phenanthrene *either* in a concerted manner (144) with the dinitrogen tetraoxide in the alternative ONO-NO_2 form[118] or by the rapid collapse within the solvent cage of the radical pair (145) formed by reaction of dinitrogen tetraoxide and phenanthrene, Figure 4.5. These necessarily *cis* forms lead to the *cis* -nitrito nitrate compound (146) and subsequent oxidation would then give *cis* -nitro nitrate (136), Scheme 4.5.

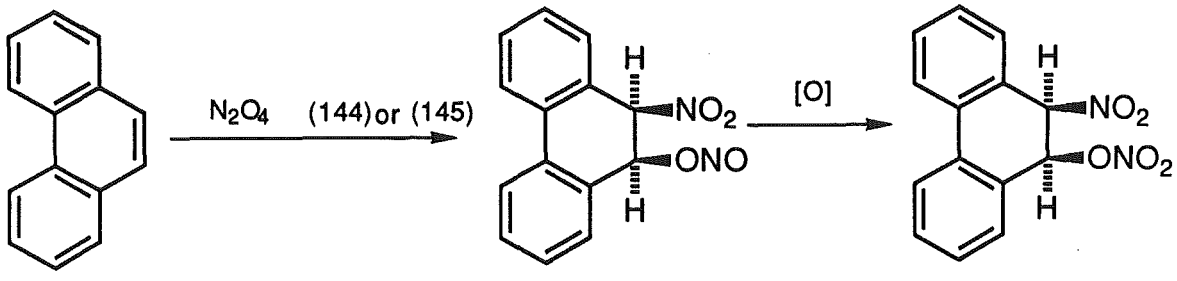


(144)



(145)

Figure 4.5



(130) Scheme 4.5 (146) (136)

4.2.2 Gas-liquid Chromatography of the Nitro Nitrates (135) and (136), and of Product Mixtures.

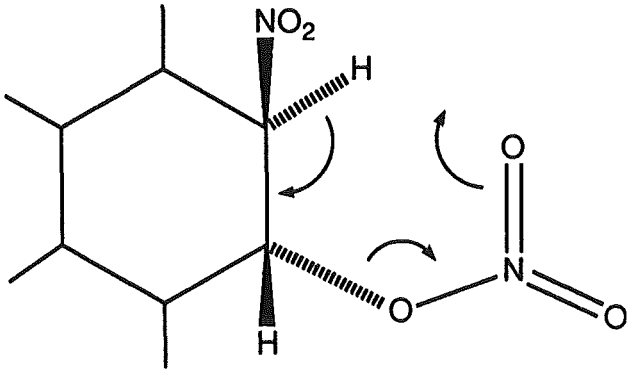
In the literature, the products of the reactions of PAHs with nitrogen dioxide are commonly analysed by gas-liquid chromatography (g.l.c.), by GCMS, or by both. As was mentioned in the introduction to this Chapter there are contradictory reports in the literature as to the nitration products of phenanthrene (130) with some authors reporting the formation of only nitrophenanthrenes and other authors also reporting the presence of the dimeric nitro nitrate (132). The presence of the two nitro nitrates (135) and (136) as products in these reactions has not been reported previously. With these observations in mind it was clearly of interest to study the behaviour of these materials under g.l.c. conditions suitable for the analysis of mixtures of mononitrophenanthrenes. The results of this investigation is presented in Table 4.2.

For the dimeric nitro nitrate (132) the resultant g.l.c. output was relatively simple with two major peaks corresponding to phenanthrene (130) and 9-nitrophenanthrene (131), with only a minor peak corresponding to unknown (151). Presumably the dimeric nitro nitrate (132) is undergoing pyrolytic elimination reactions in the inlet port of the gas chromatograph giving phenanthrene (130) and 9-nitrophenanthrene as the major products. In contrast the g.l.c. trace of *trans* -nitro nitrate (135) was complicated, containing eight peaks, two of which were large, 9-nitrophenanthrene (131) and unknown (151). The phenanthrene (130) peak in this case was small. That there was a high yield of 9-nitrophenanthrene (131) from the pyrolysis of *trans* -nitro nitrate (135) is explained when the likely transition state involved in the pyrolytic elimination is examined, Figure 4.6. The stereochemical relationship between H(10) and the nitrate oxygen is such that the cyclic transition state necessary for elimination is readily achieved. The products of such an elimination reaction would be 9-nitrophenanthrene (131) and $HONO_2$.[2]

Table 4.2. G.l.c. results for the product mixtures from phenanthrene/nitrogen dioxide reactions, dimeric nitro nitrate (132), and *trans* -nitro nitrate (135).

	product mixtures			compounds	
	reaction	reaction	reaction		
peak	1.4 M [a]	5.6×10^{-1} M [a]	5.6×10^{-2} M [a]	(132)	(135)
unknown (147)	-	-	-	-	2%
Phenanthrene (130)	1%	4%	0.6%	59%	2%
unknown (148)	-	0.1%	0.2%	-	2%
unknown (149)	0.3%	0.6%	0.9%	-	9%
unknown (150)	0.3%	0.3%	0.2%	-	1%
unknown (151)	7%	9%	13%	4%	19%
9-Nitrophenanthrene (131)	65%	63%	57%	37%	60%
unknown (152)	-	-	-	-	5%
1-Nitrophenanthrene (134)	14%	12%	14%	-	-
3-Nitrophenanthrene (133)	12%	11%	13%	-	-

[a] Concentration of phenanthrene (130) in benzene solution.



(135) Figure 4.6

Some comment can be made on the results of the g.l.c. of the three product mixtures in the light of the g.l.c. results for the dimeric nitro nitrate (132) and the *trans* -nitro nitrate (135). Although the traces were complicated, it is apparent that the three addition products [(132), (135) and (136)] all undergo pyrolytic elimination reactions to give additional 9-nitrophenanthrene (131), some phenanthrene (130) and unknown (151). Because of the relative size of the peak due to unknown (151) in both the output from the *trans* -nitro nitrate (135) and the three reaction products, attempts were made to identify the material by GCMS under E.I. conditions. In the event the mass spectrum obtained for the unknown (151) gave peaks at m/e 210, 181, 165, 153, 152 and 76, but its identity remains uncertain.

In the light of the above results it is clear that g.l.c. analysis of product mixtures from the reaction of phenanthrene (130) with nitrogen dioxide gave results at odds with the known composition of the mixtures determined by ^{1}H n.m.r. spectroscopy. The common use of g.l.c. to determine the composition of nitration product mixtures is almost certainly the cause of the confusion in the reported products of the reaction of phenanthrene with nitrogen dioxide, see Section 4.1. At this time it is unclear whether or not this problem arises for other substrates.

Chapter 5.
Experimental.

5.1 Apparatus, Materials and Instrumentation.

Infrared spectra were recorded on a Shimadzu IR-27G or a Pye-Unicam SP3 spectrometer as: thin films, Nugol mulls or KBr disks. Ultraviolet absorption spectra were obtained using a Varian DMS-100 spectrometer with chloroform as solvent. Mass spectra were recorded on a Kratos MS80RFA mass spectrometer.

^{1}H n.m.r. and ^{13}C n.m.r. spectra were obtained in deuterochloroform with tetramethylsilane as internal reference on a Varian XL-300 F.T. N.M.R. Spectrometer. Chemical shifts are expressed as parts per million (ppm) downfield from TMS and are given as position (δ), multiplicity (s=singlet, d=doublet, m=multiplet and, br=broad), relative integral (H=1 and Methyl=3), and coupling constant (J, Hz).

Microanalysis were carried out by the Analytical Laboratory, University of Otago.

Melting points were carried out in open tubes and are uncorrected.

Preparative scale chromatography was carried out using a Chromatotron (Harrison and Harrison), a preparative, centrifugally accelerated, radial thin-layer chromatograph. Silica gel used on Chromatotron plates was Merck 60 P.F.254. Chromatography was carried out at room temperature (*i.e.* solvents and the apparatus at ambient temperature) or at low temperature (*i.e.* in the cold room, 8°, with the solvent chilled to -78° by passage through dry ice/acetone).

Normal phase HPLC was carried out using a Shimadzu High Performance Liquid Chromatograph (LC-4A) fitted with a UV Spectrophotometric Detector (SPD-2AS) and an Alltech CN 10 Micron Preparative HPLC Column.

Reagents used were either of analytical grade (AR) or were purified and dried according to standard methods[119].

5.2 Experimental To Chapter 2.

5.2.1 General Reaction Conditions for Treatment of Phenols and Related Compounds with Nitrogen Dioxide.

A solution of the substrate (100 mg/ml) in the appropriate solvent was deoxygenated by a stream of nitrogen for 10 minutes. Nitrogen dioxide was then bubbled through the solution at the given temperature for 30 s, and the mixture was stirred under an atmosphere of nitrogen dioxide for 1 h. After this time the solvent and excess nitrogen dioxide were removed under reduced pressure at 5° to give a mixture of products. The composition of each reaction mixture was determined by ^{1}H n.m.r. (300 MHz). The mixtures were separated by either chromatography on a Chromatotron silica gel plate or by a combination of trituration and chromatography.

5.2.2 Reactions of 3,4,5-Trimethylphenol (58) and Related Compounds.

Preparation of 3,4,5-Trimethylphenol (58).

3,4,5-Trimethylphenol (58) was achieved by the method of Young[120]. Isophorone (50 g) was slowly added (1 hour) to a solution of cupric chloride dihydrate (12.7 g), glacial acetic acid (60 ml) and concentrated hydrochloric acid (12 ml) in water (30 ml) at 70°. Air (2000 ml min^{-1}) was bubbled into the mixture as the isophorone was added. The reaction was then left under these reaction conditions (temperature and air flow) for a total of eight hours. The phenol was obtained by extraction with ether to give:

3,4,5-Trimethylphenol (58) m.p. 108-109° (Lit.[121] 108°). υ_{max} (Nujol) 3255 cm^{-1} OH; ^{1}H n.m.r. ($CDCl_3$) δ 2.06, s,4-Me; 2.20, s, 3- and 5- methyls; 4.75, br s, OH; 6.30, s, H2 H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.46, 4-Me; 20.57, 3- and 5- methyls; 114.35, C2 C6; 127.13, C4; 137.77, C3 C5; 152.61, C1. λ_{max} ($CHCl_3$) 284 nm (ε 1080).

Reaction of 3,4,5-Trimethylphenol (58) with Nitrogen Dioxide in Benzene at 5°.

Reaction of 3,4,5-trimethylphenol (58) (500 mg), as above, gave an orange solid (970 mg), shown to be a mixture (*c.* 1:1.3:1.1) of trinitrocyclohexa-2,5-dienone (59), nitrocyclohexa-2,5-dienone (60) and the dinitrocyclohexa-2,5-dienone (61).

Trituration of the above mixture with cold ether left a colourless solid (250 mg). Recrystallisation from cold dichloromethane/pentane gave:

3,4,5-Trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59), m.p. 137-138° (dec) (Found C, 39.9; H, 3.3; N, 15.0. $C_9H_9N_3O_7$ requires C, 39.9; H, 3.4; N, 15.5%). υ_{max} (Nujol) 1718, conjugated ketone; 1670, C=C; 1570 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.11, s, 4-Me; 2.12, s, 3-, 5- methyls. λ_{max} ($CHCl_3$) 240 nm (ε 14700).

The ether soluble fraction after removal of the solvent under reduced pressure gave a residue (750 mg) that was shown to be a mixture (*c.* 1:1.5:9) of trinitrocyclohexa-2,5-dienone (59), nitrocyclohexa-2,5-dienone (60) and dinitrocyclohexa-2,5-dienone (61). Chromatography of this mixture on a Chromatotron silica gel plate gave, in order of elution:

3,4,5-Trimethyl-2-nitrophenol (62) m.p. 100-101° (Lit.[81]. 96-98°). υ_{max} (Nujol) 3410, OH; 1514, 1354 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.16, s, 2.30, s, 2.43, 3-, 4-, 5- methyls; 6.81, s, H; 9.38, br s, OH. This compound was not present initially but is formed during the chromatography by rearrangement of 3,4,5-trimethyl-4-nitrocyclohexa-2,5-dienone (60).

3,4,5-Trimethyl-2,6-dinitrophenol (63) m.p. 123.5-124.5° (Found C, 47.6; H, 4.8; N, 12.4. $C_9H_{10}N_2O_5$ requires C, 47.8; H, 4.5; N, 12.4%). υ_{max} (Nujol) 3250, OH; 1538 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.27, s, 4-Me; 2.39, s, 2-, 6- methyls, 9.52, br s, OH. ^{13}C n.m.r. ($CDCl_3$) δ 15.97, 4-Me; 16.85, 3-, 5- methyls; 129.66, C4; 135.24, C2 C6; 137.95, C3 C5; 143.10, C1. λ_{max} ($CHCl_3$) 284, 350 nm (ε 9900, 6400).

3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) m.p. 64.5-66° (Lit.[122] 63-64°) . υ_{max} (Nujol) 1682, conjugated ketone; 1642, C=C; 1549 cm^{-1} NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.88, s, 4-Me; 1.99, d ($J_{3\text{-Me,H2};\ 5\text{-Me,H6}}$ 1.39 Hz), 3- 5- methyls; 6.23, m, H2, H5. λ_{max} ($CHCl_3$) 240 nm (ε 11800).

3,4,5-Trimethyl-2,4-dinitrocyclohexa-2,5-dienone (61) ^{1}H n.m.r. ($CDCl_3$) δ 1.89, s, 1.99, s, 3-, 4- methyls; 2.02, d ($J_{5\text{-Me, H6}}$ 1.3 Hz), 5-Me; 6.27, m, H; was present initially but decomposed during chromatography.

Reaction of 3,4,5-Trimethylphenol (58) with Nitrogen Dioxide in Dichloromethane at 5°.

Reaction of 3,4,5-trimethylphenol (58) (500 mg), as above, gave an orange oil (948 mg) shown (^{1}H n.m.r.) to be a mixture (*c.* 1:1.3:1.1) of trinitrocyclohexa-2,5-dienone (59), nitrocyclohexa-2,5-dienone (60) and the dinitrocyclohexa-2,5-dienone (61).

Reaction of 3,4,5-Trimethylphenol (58) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of 3,4,5-trimethylphenol (58) (200 mg), as above, gave an orange oil (390 mg) shown (^{1}H n.m.r.) to be a mixture (*c.* 1.3:2.2:1) of trinitrocyclohexa-2,5-dienone (59), nitrocyclohexa-2,5-dienone (60) and the dinitrocyclohexa-2,5-dienone (61).

Rearrangement of 3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) in (D)-Chloroform.

A solution of nitrocyclohexa-2,5-dienone (60) (240 mg) in (D)-chloroform (1 ml) was stored at 25° and the ^{1}H n.m.r. spectrum monitored at appropriate intervals over 48 hours. At the end of this time the solution was an equilibrium mixture (*c.* 1:1.3) of the nitrophenol (62) and the nitrocyclohexa-2,5-dienone (60). This mixture was separated on a Chromatotron silica gel plate and gave in order of elution:
3,4,5-Trimethyl-2-nitrophenol (62), identical with authentic material.
3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60), identical with authentic material.

Attempted Reaction of 3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) with Nitrogen Dioxide in Benzene at 5°.

Reaction of the 4-nitrocyclohexa-2,5-dienone (60) (10 mg), as above, gave an orange oil (25 mg) shown (^{1}H n.m.r.) to be unreacted 4-nitrocyclohexadienone (60).

Attempted Reaction of 3,4,5-Trimethyl-4-nitrocyclohexa-2,5-dienone (60) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of the 4-nitrodienone (60) (50 mg), as above, gave an orange oil (35 mg) shown (^{1}H n.m.r.) to be essentially unreacted nitrocyclohexa-2,5-dienone 60).

Reaction of 3,4,5-Trimethyl-2-nitrophenol (62) with Nitrogen Dioxide in Benzene at 5°.

Reaction of nitrophenol (62) (170 mg), as above, gave an orange solid (286 mg), shown (^{1}H n.m.r.) to be a mixture (*c.* 1.4:1) of the trinitrocyclohexa-2,5-dienone (59) and the dinitrocyclohexa-2,5-dienone (61). Trituration gave trinitrocyclohexa-2,5-dienone (59), identical with authentic material, but attempts to obtain pure dinitrocyclohexa-2,5-dienone (61) from this mixture were unsuccessful.

Reaction of 3,4,5-Trimethyl-2-nitrophenol (62) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of nitrophenol (62) (50 mg), as above, gave an orange solid (50 mg), shown (^{1}H n.m.r.) to be a mixture (*c.* 1:1.1) of the trinitrocyclohexa-2,5-dienone (59) and dinitrocyclohexa-2,5-dienone (61).

Reaction of 3,4,5-Trimethyl-2,6-dinitrophenol (63) with Nitrogen Dioxide in Benzene at 5°.

Reaction of 3,4,5-trimethyl-2,6-dinitrophenol (63) (100 mg), as above, gave a colourless solid (104 mg), shown (^{1}H n.m.r.) to be essentially pure 3,4,5-trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59).

Reaction of 3,4,5-Trimethyl-2,6-dinitrophenol (63) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of 3,4,5-trimethyl-2,6-dinitrophenol (63) (40 mg), as above, gave a colourless solid (54 mg), shown (^{1}H n.m.r.) to be essentially pure 3,4,5-trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59).

Attempted Reaction of 3,4,5-Trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59) with Nitrogen Dioxide in Benzene.

Treatment of trinitrocyclohexa-2,5-dienone (59) (100 mg), as above, gave a colourless solid (104 mg) shown (^{1}H n.m.r.) to be essentially pure 3,4,5-trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59).

Isomerisation of 3,4,5-Trimethyl-2,4,6-trinitrocyclohexa-2,5-dienone (59) in (D)-Chloroform; Preparation of 4-Hydroxy-3,4,5-trimethyl-2,6-dinitrocyclohexa-2,5-dienone (69).

A solution of the trinitrocyclohexa-2,5-dienone (59) (180 mg) in (D)-chloroform (2 ml) was stored at 40° and the ^{1}H n.m.r. spectrum was monitored at appropriate intervals over 24 hours. At the end of this time the solvent was removed under reduced pressure. The colourless solid obtained (175 mg) was recrystallised from cold dichloromethane/pentane to give:

4-Hydroxy-3,4,5-trimethyl-2,6-dinitrocyclohexa-2,5-dienone (69) m.p. 184-185° (dec.) ($M^{+\cdot}$ 226.058860. $C_9H_{10}N_2O_5$ = 226.058965.). υ_{max} (Nujol) 3470, OH; 1695, conjugated ketone; 1672, 1643, C=C; 1562 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.67, s, 4-Me; 2.23, s, 3-, 5- methyls; 2.49, br s, OH. λ_{max} ($CHCl_3$) 242 nm (ε 22300).

Attempted Reaction of 4-Hydroxy-3,4,5-trimethyl-2,6-dinitrocyclohexa-2,5-dienone (69) with Nitrogen Dioxide in Benzene at 5°.

A suspension of hydroxydinitrocyclohexa-2,5-dienone (69) (70 mg) treated with nitrogen dioxide, as above, gave a colourless solid (80 mg), shown (^{1}H n.m.r.) to be unreacted hydroxydinitrocyclohexa-2,5-dienone (69).

5.2.3 Reactions of 3,4-Dimethylphenol (71) and Related Compounds.

Reaction of 3,4-Dimethylphenol(71) with Nitrogen Dioxide in Benzene at 5°.

Reaction of 3,4-dimethylphenol (71) (500 mg), as above, gave an orange oil (935 mg) shown to be a mixture (*c.* 6.7:3.2:1:trace) of 3,4-dimethyl-2,6-dinitrophenol (72), 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73), 4-hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74), and an unidentified compound. Chromatography using a Chromatotron silica gel plate at low temperature gave, in order of elution:

3,4-Dimethyl-2,6-dinitrophenol (72) m.p. 126.5 - 127.5 (Lit.[85] 126-127°). υ_{max} (Nujol) 3230, OH; 1542, 1465 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.29, s, 4-Me; 2.35, s, 3-Me, 8.02, s, H5; 10.67, br s, OH. ^{13}C n.m.r. ($CDCl_3$) δ 15.33, 4-Me; 19.39, 3-Me; 129.72, C5; 129.72, C4; 131.65, C6; 134.57, C2; 139.28, C3; 145.21, C1. λ_{max} ($CHCl_3$) 280, 356 nm (ε 7720, 4570).

3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) m.p. 76-77° (dec.) [Lit.[82] 76° (dec.)]. υ_{max} (Nujol) 1664, C=O; 1638, C=C; 1545 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.91, s, 4-Me; 2.04, d ($J_{3\text{-Me,H2}}$ 1.4 Hz), 3-Me; 6.27, m, H2; 6.40, d of d ($J_{H6,H5}$ 9.9 Hz, $J_{H6,H2}$ 1.7 Hz), H6; 6.86, d ($J_{H5,H6}$ 10.0 Hz), H5. ^{13}C n.m.r. could not be obtained. λ_{max} ($CHCl_3$) 241, 362 nm (ε 7500, 100).

4-Hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74) decomposed during chromatography and was not isolated from this reaction.

The unknown compound also decomposed during chromatography and could not be isolated.

Reaction of 3,4-Dimethylphenol (71) with Nitrogen Dioxide in Dichloromethane at 5°.

Reaction of 3,4-dimethylphenol (71) (500 mg), as above, gave an orange oil (900 mg) shown to be a mixture (*c.* 1.3:1.8:1) of 3,4-dimethyl-2,6-dinitrophenol (72), 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73) and 4-hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74).

Reaction of 3,4-Dimethylphenol (71) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of 3,4-dimethylphenol (71) (500 mg), as above, gave an orange oil (921 mg) shown to be a mixture (*c.* 1.2:1:trace) of: 3,4-dimethyl-2,6- dinitrophenol (72), 3,4-dimethyl-4-nitrocyclohexa-2,5-dienone (73) and an unknown compound.

Attempted Reaction of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) with Nitrogen Dioxide in Benzene at 5°.

Attempted reaction of the nitrodienone (73) (10 mg), as above, gave an orange oil (8 mg) shown to be unchanged nitrodienone (73).

Reaction of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) with Nitrogen Dioxide in Benzene at 20°.

Reaction of the nitrodienone (73) (50 mg), as above, gave an orange oil (75 mg) shown to be a mixture (*c.* 1:4.1:2.6) of dinitrophenol (72), unchanged 4-nitro-dimethyldienone (73) and hydroxydienone (74).

Attempted reaction of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) with Nitrogen Dioxide in Dichloromethane at -23°.

Attempted reaction of 4-nitrodimethyldienone (73) (10 mg), as above, gave an orange oil (35 mg) shown to be essentially unchanged 4-nitrodimethyldienone (73).

Preparation of 4,5-Dimethyl-2-nitrophenol (76), 3,4-Dimethyl-2-nitrophenol (75), and 3,4-Dimethyl-2,6-dinitrophenol (72).

These three compounds were prepared by the method of Holler *et al.*[85]
A solution of nitric acid (1.42 s.g, 10 ml) and glacial acetic acid (50 ml) was added dropwise to a stirred solution of 3,4-dimethylphenol (71) in glacial acetic acid (100 ml.). The temperature was maintained between 15° and 20°. After the final addition of the nitric acid, the reaction mixture was stored for 15 minutes. The nitration was terminated by pouring the reaction mixture into iced water (1 l.) and then adding urea (10 g).

The mixture was then steam distiled and the distillate was extracted with dichloromethane. After drying over $MgSO_4$, the solvent was removed under reduced

pressure to give solid (5 g) which was shown (^{1}H n.m.r. and infrared spectra) to be a mixture (*c.* 1:1:2) of 4,5-dimethyl-2-nitrophenol (76), 3,4-dimethyl-2-nitrophenol (75), and 3,4-dimethyl-2,6-dinitrophenol (72). Chromatography of this mixture on a Chromatotron silica gel plate gave, in order of elution:

4,5-Dimethyl-2-nitrophenol (76) m.p. 88-89° (dec.) [Lit.[85] 86.7-87.7° (dec.)]. υ_{max} (KBr) 3160, OH; 1527, 1426 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 2.24, s, 5-Me; 2.30, s, 4-Me; 6.93, s, H6; 7.84, s, H3; 10.46, OH. ^{13}C n.m.r.($CDCl_3$) δ 18.76, 4-Me; 20.39, 5-Me; 120.03, C6; 124.61, C3; 129.29, C4; 142.69, C2: 148.90, C5: 153.32, C1. λ_{max} ($CHCl_3$) 293, 368 nm (ε 7260, 2500).

3,4-Dimethyl-2-nitrophenol (75) m.p 73-74°. [Lit.[123] 71-72° (dec)]. υ_{max} (KBr) 3400, OH; 1530 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 2.27, s, 4-Me; 2.41, s, 3-Me; 6.89, d ($J_{H5,H6}$ 8.5 Hz), H5; 7.26, d ($J_{H6,H5}$ 8.5 Hz), H6. ^{13}C n.m.r.($CDCl_3$) δ 16.94, 4-Me; 20.00, 3-Me; 115.95, C6; 130.00, C4; 133.34, C3; 134.52, C2; 136.46, C5; 151.69, C1. λ_{max} ($CHCl_3$) 286, 368 nm (ε 9750, 4650).

Reaction of 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in Benzene at 5°.

Reaction of 3,4-dimethyl-2-nitrophenol (75) (100 mg), as above, gave an orange oil (154 mg) shown (^{1}H n.m.r.) to be (*c.* 6.6:3.6:1) of dinitrophenol (72), hydroxydinitrodienone (74) and an unknown compound.

Reaction of 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of the 3,4-dimethyl-2-nitrophenol (75) (65 mg), as above, gave an orange oil (87 mg) shown (^{1}H n.m.r.) to be essentially pure dinitrophenol (72).

Reaction of 4,5-Dimethyl-2-nitrophenol (76) with Nitrogen Dioxide in Benzene at 5°.

Reaction of the 4,5-dimethyl-2-nitrophenol (76) (500 mg), as above, gave an orange oil (830 mg) shown (^{1}H n.m.r.) to be (*c.* 2.4:1) of dinitrophenol (72) and 4-hydroxydienone (74).

Reaction of 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in Benzene at 20°.

Reaction of the 3,4-dimethyl-2-nitrophenol (75) (300 mg), as above, gave a colourless oil (391 mg) shown (^{1}H n.m.r.) to be essentially pure hydroxydinitrodienone (74). Crystallization from dichloromethane/pentane gave pure material:

4-Hydroxy-3,4-dimethyl-2,6-dinitrocyclohexa-2,5-dienone (74) m.p 108-109°. (Found $M^{+\bullet}$ 228.0381. $C_8H_8N_2O_6$ requires 228.0382). υ_{max} (KBr) 3500, OH; 1690 conjugated ketone; 1540, 1370 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.71, s, 4-Me; 2.20, s, 3-Me; 7.68, s, H; 7.36, s, OH. ^{13}C n.m.r. could not be determined because the material was only sparingly soluble in common n.m.r. solvents. λ_{max} ($CHCl_3$) 240, 358 nm (ε 7050, 4400).

Reaction of 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in Dichloromethane at -23°.

Reaction of the 3,4-dimethyl-2-nitrophenol (75) (500 mg), as above, gave an orange solid (750 mg) shown (^{1}H n.m.r.) to be essentially pure dinitrophenol (72).

Reaction of 3,4-Dimethyl-2,6-dinitrophenol (72) with Nitrogen Dioxide in Benzene at 5°.

Reaction of the 3,4-dimethyl-2,6-dinitrophenol (72) (200 mg), as above, gave an orange oil (330 mg) shown (^{1}H n.m.r.) to be a mixture (*c.* 1:2:trace) of: dinitrophenol (72), hydroxydinitrodienone (74) and an unknown compound.

Attempted reaction of 3,4-Dimethyl-2,6-dinitrophenol (72) with Nitrogen Dioxide in Dichloromethane at -23°.

Attempted reaction of the 3,4-dimethyl-2,6-dinitrophenol (72) (400 mg), as above, gave a yellow solid (414 mg) shown (^{1}H n.m.r.) to be essentially pure dinitrophenol (72).

Rearrangement of 3,4-Dimethyl-4-nitrocyclohexa-2,5-dienone (73) in (D)-chloroform at 23°.

Recrystallised nitrodienone (73) (5 mg) was dissolved in (D)-chloroform (0.5 ml) and the changing composition of the solution was followed by ^{1}H n.m.r. spectroscopy. The first spectrum showed a mixture (*c.* 1:trace) of nitrodienone (73) and 2-nitro-

4,5-dimethylphenol (76). After 22 hours at 23° the rearrangement was complete and the solution contained a mixture (*c.* 5.8:1) of 4,5-dimethyl-2-nitrophenol (76) and 3,4-dimethyl-2-nitrophenol (75).

Reaction of 4,5-Dimethyl-2-nitrophenol (76) and 3,4-Dimethyl-2-nitrophenol (75) with Nitrogen Dioxide in (D)-Chloroform at Low Temperatures.

General Procedure: A cold (-50°) solution of nitrogen dioxide in (D)-chloroform (0.25 ml) was added to a solution of the phenol (5 mg) in (D)-chloroform (0.25 ml) at -78°; the nitrogen dioxide concentration was such that a large excess (estimated > 20 mole equivalents, relative to the reacting phenol) of nitrogen dioxide was used. The cold (< -60°) resulting mixture was mixed in a vortex mixer, and the reactions were followed by ^{1}H n.m.r. spectroscopy at appropriate reaction temperatures.

Reaction of 3,4-Dimethyl-2-nitrophenol (75) at -60°.

The reaction was relatively fast, with *c.* 78% conversion of the phenol (75) into products after 5 minutes. At that time the solution was a mixture (*c.* 1.2:1) of 3,4-dimethyl-2,6-dinitrophenol (72) and a new compound; identified by its ^{1}H n.m.r. spectrum as 3,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienone (77); ^{1}H n.m.r. ($CDCl_3$) δ 2.09, s, 2.13, s, 3- and 4- methyls; 6.64, d ($J_{H6,H5}$ 10 Hz), H6; 7.09, d ($J_{H5,H6}$ 10 Hz), H5.

Reaction of 4,5-Dimethyl-2-nitrophenol (76) at -23°.

The reaction was slow, with *c.* 16% conversion of the phenol (76) into products after 15 minutes and *c.* 46% conversion into products after 1 hour. At that time the solution was a mixture (*c.* 1.4:1) of 3,4-dimethyl-2,6-dinitrophenol (72) and a new compound; identified by its ^{1}H n.m.r. spectrum as 4,5-dimethyl-2,5-dinitrocyclohexa-2,4-dienone (76); ^{1}H n.m.r. ($CDCl_3$) δ 2.09, s,4-Me; 2.16, d ($J_{5\text{-}Me,H6}$ 1.4 Hz), 5Me; 6.44, q ($J_{H6,5\text{-}Me}$ 1.4 Hz), H6; 7.55, s, H3.

5.2.4 Reactions of 4-Methylphenol (88) and Related Compounds.

Reaction of 4-Methylphenol (88) with Nitrogen Dioxide in Benzene at 5°.

Treatment of 4-methylphenol (88) (500 mg), as above, gave an orange oil (950 mg) shown to be a mixture (*c.* trace:1:3.4) of 4-methylphenol (88), 4-nitrodienone (89) and dinitrophenol (90).

The 4-nitrodienone (89) decomposed on the Chromatotron silica gel plate and was identified by comparison with the known ^{1}H n.m.r. spectrum (see below).

4-Methyl-2,6-dinitrophenol (90). m.p. 82-83° (Lit.[86] 84°) υ_{max} (KBr) 3100, OH; 1530, 1360 cm^{-1}, nitro. ^{1}H n.m.r. ($CDCl_3$) δ 2.45, s, 4-Me; 8.14, s, H3, H5; 11.28, s, OH. ^{13}C n.m.r. ($CDCl_3$) δ 20.25, Me; 129.41, C4; 131.68, C3, C5; 134.53, C2, C6; 147.40, C1. λ_{max} ($CHCl_3$) 242, 361 nm (ε 13400, 7500).

Reaction of 4-Methylphenol (88) with Nitrogen Dioxide in Dichloromethane at 5°.

Treatment of 4-methylphenol (88) (500 mg) as above, gave an orange oil (929 mg) shown to be a mixture (*c.* 1:4.2) of 4-nitrodienone (89) and dinitrophenol (90).

Reaction of 4-Methylphenol (88) with Nitrogen Dioxide in Dichloromethane at -23°.

Treatment of 4-methylphenol (88) (500 mg), as above, gave an orange oil (921 mg) shown to be a mixture (*c.* 4:1:7.5) of 4-nitrodienone (89), 4-methyl-2-nitrophenol (164) and dinitrophenol (90). Chromatography gave:

4-Methyl-2-nitrophenol (164) m.p. 32-33° (Lit.[87] 32-33°). υ_{max} (KBr) 3270, OH; 1530, 1302 cm^{-1}, nitro. ^{1}H n.m.r. ($CDCl_3$) δ 2.35, s, Me; 7.06, d ($J_{H6,H5}$ 8.6 Hz), H6; 7.40, d of d ($J_{H5,H6}$ 8.7 Hz, $J_{H5,H3}$ 2.2 Hz), H5; 7.90, d ($J_{H3,H5}$ 2.2 Hz), H3. ^{13}C n.m.r. ($CDCl_3$) δ 20.24, Me; 118.60, C4; 119.63, C6; 124.36, C3; 138.73, C5; 142.69, C2; 153.13, C12. λ_{max} ($CHCl_3$) 239, 280, 370 nm (ε 4100, 8200, 3800).

4-Methyl-2,6-dinitrophenol (90), identical with authentic material.

Preparation of 4-Methyl-4-nitrocyclohexa-2,5-dienone (89).

This compound was prepared from 4-methylphenylacetate by the method of Barnes *et. al.*[122]

4-Methylphenylacetate (10 g) was prepared from 4-methylphenol (88) (25 g) by dissolving the phenol (88) in a 10% sodium hydroxide solution (160 ml), adding acetic anhydride (30 ml) and then isolating the product by extraction with dichloromethane.[124]

4-Methyl-4-nitrocyclohexa-2,5-dienone (89) was prepared from 4-methylphenylacetate (10 g) by adding nitric acid (density 1.42, 6.2 ml) over twenty minutes to a stirred solution of 4-methylphenylacetate (10 g) in acetic anhydride (25 ml). The temperature was held between -5° and 0° throughout. Reaction was then allowed to proceed for a further 10 minutes. Chilled methanol (30 ml) was added and the temperature was lowered to -78° in an acetone/dry ice bath. The 4-nitrodienone (89) precipitated as colourless crystals which were isolated by suction filtration. The yield was 2.15 g (21%).

4-Methyl-4-nitrocyclohexa-2,5-dienone (89). ^{1}H n.m.r. ($CDCl_3$) δ 1.95, s, Me; 6.43, m, H2, H6; 7.19, m, H3, H5 (The two multiplets are doublets,*J* 10.4 Hz, with fine structure). Lit.[122]: ^{1}H n.m.r. ($CDCl_3$) δ 1.95, s,4-Me; 6.35, d ($J_{H2,H3}$ and $J_{H6,H5}$ 10 Hz); H2, H6; 7.15, d ($J_{H3,H2}$ and $J_{H5,H6}$ 10 Hz); H3, H5.

Attempted Reaction of 4-Methyl-4-nitrocyclohexa-2,4-dienone (89) with Nitrogen Dioxide in Benzene at 5°.

Treatment of 4-nitrodienone (89) (310 mg), as above, gave an orange oil shown to be essentially unchanged 4-nitrodienone (89) (305 mg).

Attempted Reaction of 4-Methyl-4-nitrocyclohexa-2,5-dienone (89) with Nitrogen Dioxide in Dichloromethane at -23°.

Treatment of 4-nitrodienone (89) (200 mg), as above, gave an orange oil shown to be essentially unchanged 4-nitrodienone (89) (225 mg).

Reaction of 4-Methyl-2-nitrophenol (164) with Nitrogen Dioxide in Benzene at 5°.

Treatment of the phenol (164) (120 mg), as above, gave a oily solid (146 mg) shown to be a mixture (*c.* 11.5:1) of dinitrophenol (90) and an unknown compound which could not be isolated.

Reaction of 4-Methyl-2-nitrophenol (164) with Nitrogen Dioxide in Benzene at -23°.

Treatment of the phenol (164) (115 mg), as above, gave a oily solid (120 mg) shown to be a mixture (*c.* 1:24) of 4-Methyl-2-nitrophenol (164) and dinitrophenol (90).

Attempted Reaction of 4-Methyl-2,6-dinitrophenol (90) with Nitrogen Dioxide in Benzene at 5°.

Treatment of dinitrophenol (90) (25 mg), as above, gave an orange oil shown to be essentially unchanged dinitrophenol (90) (30 mg).

Attempted Reaction of 4-Methyl-2,6-dinitrophenol (90) with Nitrogen Dioxide in Dichloromethane at -23°.

Treatment of the dinitrophenol (90) (25 mg), as above, gave an orange oil shown to be essentially the unchanged dinitrophenol (90) (22 mg).

Reaction of 4-Methyl-2-nitrophenol (164) with Nitrogen Dioxide in (D)-Chloroform at -23°.

A cold (-50°) solution of nitrogen dioxide in (D)-chloroform (0.25 ml) was added to a solution of the phenol (164) (5 mg) in (D)-chloroform (0.25) at -78°; the nitrogen dioxide concentration was such that a large excess (estimated > 20 mole equivalents, relative to the reacting phenol) of nitrogen dioxide was used. The cold (< -60°) resulting mixture was mixed in a vortex mixer, and the ensuing reactions were followed by ^{1}H n.m.r. spectroscopy at appropriate temperatures.

The reaction was slow, with *c.* 3% conversion of the phenol (164) into products after 5 minutes and *c.* 39% conversion after 1 hour. At that time the solution was a mixture (*c.* 1.6:1) of 4-methyl-2,6-dinitrophenol (90) and a new compound, identified by its ^{1}H n.m.r. spectrum as 4-methyl-2,4-dinitrocyclohexa-2,5-dienone (165), ^{1}H n.m.r. ($CDCl_3$) δ 2.37, s, 4-Me; 6.57, d ($J_{H6,H5}$ 10 Hz), H6; 7.31, d of d ($J_{H5,H6}$ 10 Hz, $J_{H5,H3}$ 3 Hz), H5; 7.82, d ($J_{H3,H5}$ 3 Hz), H3.

5.3 Experimental To Chapter 3.

5.3.1 Reactions of 3,4,5-Trimethylbiphenyl (91) and Related Compounds.

Preparation of 3,4,5-Trimethylaniline.

3,4,5-Trimethylaniline was prepared from isophorone by the method of Beringer and Ugelow.[125]

Treatment of isophorone (2.0 moles, 300 ml) with hydroxylamine hydrochloride (170 g) in dry pyridine (170 ml) and methanol (200 ml) for 24 hours at room temperature gave isophorone oxime (285 g, 93%).

Isophorone oxime (2.0 moles, 300 g) was added to a solution of acetyl chloride (2.0 moles, 142 ml) in acetic anhydride (1 l) and pyridine (2 moles, 161 ml). This mixture was then heated in a water bath to 65° to give a clear orange solution, which darkened after 10 minutes. The temperature was then increased to 100° and the mixture heated under reflux for one hour. The reaction was then halted by slowly adding water (1.25 l). Recrystallisation from hot water gave 3,4,5-trimethylacetanilide (144 g, 42%) in the first crop. Subsequent crops of mixed trimethylacetanilides gave a total yield of (279 g, 81%).

Hydrolysis of 3,4,5-trimethylacetanilide (100 g) in 20% sulphuric acid for two hours gave 3,4,5-trimethylaniline which precipitated when the aqueous layer was cooled and made basic with sodium hydroxide solution. Recrystallisation from light petroleum ether gave:

3,4,5-Trimethylaniline (76 g, 87%) m.p. 77-78° (Lit.[125] 78.5-79°). υ_{max} (KBr) 3450, NH_2; 2950, C-H; 1620 cm^{-1}, aromatic C=C. ^1H n.m.r. ($CDCl_3$) δ 2.04, s, 4-Me; 2.17, 3- 5- methyls; 3.36, s, NH_2; 6.34, H2 H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.25, 4-Me; 20.45, 3- 5- methyls; 114.62, C2 C6; 124.81, C4; 137.09, C3 C5; 143.46, C1. λ_{max} ($CHCl_3$) 242, 292 (ε 2740, 790). The overall yield from isophorone was 38%.

Preparation of 3,4,5-Trimethylbiphenyl (91).

A mixture of fresh *n* -amylnitrite (10 g)[124] and 3,4,5-trimethylaniline (5 g) in benzene (200 ml) was heated to induce reaction. This reaction was allowed to proceed without further heating for 20 minutes. After this time the mixture was heated under reflux for three hours.[126] The solvent was removed under reduced pressure to give an oil containing 3,4,5-trimethylbiphenyl (91). Chromatography using a Chromatotron silica gel plate gave:

3,4,5-Trimethylbiphenyl (91), m.p. (pentane) 29-30° (Found C, 91.9; H, 8.3. $C_{15}H_{16}$ requires C, 91.8; H, 8.2%). υ_{max} (liquid film) 2910, 2870, methyl; 1482, 1459 cm-1, aromatic C=C. 1H n.m.r. (CDCl3) d 2.20, s, 4-Me; 2.34, 3-, 5- methyls; 7.24, s, H2, H6; 7.29, m, H4'; 7.40, m, H3', H5'; 7.57, m, H2', H6'. ^{13}C n.m.r. ($CDCl_3$) δ 15.12, 4-Me; 20.68, 3- 5- methyls; 126.58, C4'; 126.12, 126.78, 128.38; C2, C6, C2', C3', C5', C6'; 133.99, 136.56; C3, C4, C5; 137.98, C1'; 141.11, C1. λ_{max} ($CHCl_3$) 257 nm (ε 19200).

Reaction of 3,4,5-Trimethylbiphenyl (91)with Nitrogen Dioxide in Benzene.

A solution of 3,4,5-trimethylbiphenyl (91) (500 mg) was treated with nitrogen dioxide, as above for two hours, to give an orange oil (779 mg), shown to be a mixture (*c.* 31:12:2.7:17:1:2:2) of 2-nitrobiphenyl (97), 4'-nitrobiphenyl (98), 2'-nitrobiphenyl (99), 3-nitromethylbiphenyl (100), 2-nitro-3-nitromethylbiphenyl (101), 2'-nitro-3-nitromethylbiphenyl (102) and 4'-nitro-3-nitromethylbiphenyl (103). Chromatography of this mixture on a Chromatotron silica gel plate gave, in order of elution:

3,4,5-Trimethyl-2-nitrobiphenyl (97), m.p. 117-118° (Found C, 74.3; H, 6.3; N, 5.6. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%). υ_{max} (Nujol) 1523 cm^{-1} NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.25, s, 3-Me; 2.27, s, 4-Me; 2.35, s, 5-Me; 7.06, s, H6; 7.36, m, 5 aromatic hydrogens. ^{13}C n.m.r. ($CDCl_3$) δ 15.05, 15.94, 1-, 2-methyls; 20.86, 3-Me; 127.38, 130.84, 135.93, 136.88, 138.48, C1, C1', C3, C4, C5; 127.94, 128.49, C2', C3', C5', C6', 128.00, 129.47, C4', C6; 149.67, C2.

λ_{max} ($CHCl_3$) 243, 206 nm (ε 13500, 16800). N.O.e. irradiation at δ 2.35 gave a positive difference peaks at δ 2.27 (1%) and δ 7.06 (9%).

3,4,5-Trimethyl-4'-nitrobiphenyl (98) m.p. 110-111° (X-ray crystal structure analysis, see appendix A). υ_{max} (KBr) 1505, 1320 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.24, s, 4-Me; 2.37, s, 3-, 5- methyls; 7.28, s, H2, H6; 7.71, d ($J_{H2',H3'}$ and $J_{H6',H5'}$ 9 Hz), H2', H6'; 8.27, d ($J_{H3',H2'}$ and $J_{H5',H6'}$ 9 Hz), H3', H5'. ^{13}C n.m.r. ($CDCl_3$) δ 15.46, 4-Me; 20.83, 3- 5- methyls; 123.93, C3', C5'; 126.39; C2, C6; 127.35, C2', C6'; 135.51, 136.23, C1, C4; 137.27, C3, C5; 146.61, 147.71, C1', C4'. λ_{max} ($CHCl_3$) 237, 329 nm (ε 13000, 13700). N.O.e. irradiation at δ 7.71 gave positive difference peaks at δ 7.28 (5%) and δ 8.27 (16%). Irradiation at δ 7.28 gave a positive difference peak at δ 2.37 (2%) and δ 7.71 (10%). Irradiation at δ 8.27 gave a positive difference peak at δ 7.71 (15%).

3,4,5-Trimethyl-2'-nitrobiphenyl (99) m.p. 102.5-103° (Found C, 74.7; H, 6.3; N, 5.7. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%). υ_{max} (Nujol) 1540, 1340 cm^{-1} NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.21, s, 4-Me; 2.31, s, 3-, 5- methyls; 6.97, s, H2, H6; 7.43, m, H4', H6'; 7.58, triplet of doublets ($J_{H5',H4'}$ 7.55 Hz, $J_{H5',H6'}$ 7.55 Hz, $J_{H5',H3'}$ 1.34 Hz), H5'; 7.80, doublet of doublets ($J_{H3',H4'}$ 8.17 Hz, $J_{H3',H5'}$ 1.56 Hz), H3'. ^{13}C n.m.r. could not be obtained. λ_{max} ($CHCl_3$) 246 nm (ε 20900). N.O.e. irradiation at δ 2.21 gave a positive difference peak at δ 2.31 (5%). Irradiation at δ 2.31 gave positive difference peaks at δ 2.21 (2%) and δ 6.97 (11%). Irradiation at δ 6.97 gave positive difference peaks at δ 2.31 (2%) and δ 7.43 (1%). Irradiation at δ 7.58 gave a positive difference peak at δ 7.43 (3%). Irradiation at δ 7.80 gave a positive difference peak at δ 7.43 (4%).

4,5-Dimethyl-3-nitromethylbiphenyl (100). m.p. 84-85° (Found C, 74.6; H, 6.3; N, 5.4. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%). υ_{max} (Nujol) 1543 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.32, 4-Me; 2.39, 5-Me; 5.58, CH_2NO_2; 7.42, m, H2; 7.49, m, H6; 7.35, m, H4'; 7.44, m, H3', H5'; 7.57, m, H2', H6'. ^{13}C n.m.r. ($CDCl_3$) δ 15.12, 4-Me; 20.72, 5-Me; 78.38, CH_2NO_2; 126.94, 127.42, 128.80, 130.52, C2, C6, C2', C3', C4', C5', C6'; 130.52, 135.78, 138.35, C3, C4, C5; 139.06, 140.06, C1, C1'. λ_{max} ($CHCl_3$) 254 nm (ε 30300). N.O.e. irradiation at δ 2.32 gave a positive difference peak at δ 5.58 (3%).

Irradiation at δ 2.39 gave a positive difference peak at δ 7.49 (10%). Irradiation at δ 5.58 gave positive difference peaks at δ 2.32 (3%) and δ 7.43 (10%).

4,5-Dimethyl-2-nitro-3-nitromethylbiphenyl (101) m.p. 89-90° (Found C, 63.2; H, 5.0; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%). υ_{max} (KBr) 1563, 1528, 1342 cm^{-1} NO_2 ^1H n.m.r. ($CDCl_3$) δ 2.36, s, 4-Me; 2.43, s, 5-Me; 5.55, s, CH_2NO_2; 7.37, s, H6; 7.37, m,5 aromatic hydrogens. ^{13}C n.m.r. could not be obtained. λ_{max} ($CHCl_3$) 239 nm (ε 18200). N.O.e. irradiation at δ 2.36 gave a positive difference peak at δ 5.55 (2%). Irradiation at δ 2.43 gave a positive difference peak at δ 7.37 (9%). Irradiation at δ 5.55 gave a positive difference peak at δ 2.36 (3%).

4,5-Dimethyl-2'-nitro-3-nitromethylbiphenyl (102). An oil (Found M^- 286.0944. $C_{15}H_{14}N_2O_4$ requires 286.0954.). υ_{max} (KBr) 1525, 1361 cm^{-1} NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.33, s, 4-Me; 2.36, s, 5-Me; 5.55, s, CH_2NO_2; 7.18, s, H2; 7.21, s, H6; 7.49, doublet of doublets ($J_{H6',H5'}$ 7.6 Hz, $J_{H6',H4'}$ 1.6 Hz), H6'; 7.50, triplet of doublets ($J_{H4',H3'}$; $_{H4',H5'}$ 7.8 Hz, $J_{H4',H6'}$ 1.5 Hz), H4'; 7.66, triplet of doublets ($J_{H5',H4'}$; $_{H5',H6'}$ 7.6 Hz, $J_{H5',H3'}$ 1.3HZ), H5'; 7.86, doublet of doublets ($J_{H3',H4'}$ 8.0 Hz, $J_{H3',H5'}$ 1.3 Hz), H3'. N.O.e. irradiation at δ 2.33 and δ 2.36 gave positive difference peaks at δ 5.55 (3%) and δ 7.21 (8%). Irradiation at δ 5.55 gave positive difference peaks at δ 2.33 (8%) and δ 7.18 (17%). Irradiation at δ 7.18 gave positive difference peaks at δ 5.55 (2%) and δ 7.49 (4%). Irradiation at δ 7.66 gave positive difference peaks at δ 7.49 (9%) and δ 7.50 (5%). Irradiation at δ 7.86 gave a positive difference peak at δ 7.50 (7%).

4,5-Dimethyl-4'-nitro-3-nitromethylbiphenyl (103) m.p. 120.5-122° (Found C, 62.4; H, 4.8; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%). υ_{max} (KBr) 1564, 1340 cm^{-1} NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.36, s, 4-Me; 2.43, s, 5-Me; 5.60, s, CH_2NO_2; 7.47, s, H2; 7.52, s, H6; 7.73, d ($J_{H2',H3'}$; $_{H6',H5'}$ 8.9 Hz), H2', H6'; 8.30, d ($J_{H3',H2'}$; $_{H5',H6'}$ 8.9 Hz), H3', H5'. ^{13}C n.m.r. ($CDCl_3$) δ 15.32, 4-Me; 20.77, 5-Me; 78.16, CH_2NO_2; 124.13, 127.59, 128.31, 130.61, C2, C6, C2', C3', C5', C6'; 129.26, C5; 136.59, 137.84, C3, C4; 139.01, C1; 146.45, 147.14, C1', C4'. λ_{max} ($CHCl_3$) 238, 315 nm (ε 8800, 16300). N.O.e. irradiation at δ 2.36 gave positive difference peaks at δ 2.43 (2%) and δ 5.60 (3%). Irradiation at δ 2.43 gave positive difference peaks at δ 2.36 (2%) and δ 7.52 (14%). Irradiation at δ 5.60 gave positive difference peaks at δ 2.36 (3%) and

δ 7.47 (20%). Irradiation at δ 7.73 gave positive difference peaks at δ 7.47 (9%), δ 7.52 (9%) and δ 8.30 (18%).

Reaction of 4,5-Dimethyl-3-nitromethylbiphenyl (100) with Nitrogen Dioxide in benzene,

A solution of 3-nitromethylbiphenyl (100) (170 mg) in dry benzene (5 ml) was deoxygenated by a stream of nitrogen. Nitrogen dioxide was bubbled through the stirred solution at room temperature for 30 s, and stirring was continued for 24 h while the mixture was stored at room temperature under an atmosphere of nitrogen dioxide. After 24 h the excess nitrogen dioxide was removed in a stream of nitrogen and the solvent was removed under reduced pressure to give an orange oil (240 mg), shown (^{1}H n.m.r. and infrared spectra) to be a mixture (*c.* 4.4:7.4:7.4) of 2-nitro-3-nitromethylbiphenyl (101), 2'-nitro-3-nitromethylbiphenyl (102) and 4'-nitro-3-nitromethylbiphenyl (103).

Reaction of 3,4,5-Trimethyl-2-nitrobiphenyl (97) with Nitrogen Dioxide in Benzene.

A solution of 2-nitrobiphenyl (97) (200 mg) in dry benzene (5 ml) was deoxygenated by a stream of nitrogen. Nitrogen dioxide was bubbled through the stirred solution at 7° for 30 s, and stirring was continued for 5 h while the mixture was stored at 7° under an atmosphere of nitrogen dioxide. After 5 h the excess nitrogen dioxide was removed in a stream of nitrogen and the solvent was removed under reduced pressure to give an oil (226 mg), shown (^{1}H n.m.r. and infrared spectra) to be essentially pure 2-nitrobiphenyl (97).

Reaction of 3,4,5-Trimethyl-4'-nitrobiphenyl (98) with Nitrogen Dioxide in Benzene.

A solution of 4'-nitrobiphenyl (98) (41 mg) in admixture with 2'-nitrobiphenyl (99) (20 mg) was treated with nitrogen dioxide, as above for five hours, gave an orange oil (76 mg), shown to be a mixture (*c.* 18.9:9.5:1) of 4'-nitrobiphenyl (98), 2'-nitrobiphenyl (99) and 4'-nitro-3-nitromethylbiphenyl (103).

5.3.2 Reactions of 2,3,4-Trimethylbiphenyl (92) and Related Compounds with Nitrogen Dioxide in Benzene.

Preparation of 2,3,4-Trimethylaniline by Reduction of 1,2,3-Trimethyl-4-nitrobenzene.

1,2,3-Trimethyl-4-nitrobenzene (5 g) was added to a mixture of reduced iron (5 g) and water (50 g) in a 250 ml. R.B. flask fitted with a blade stirrer and a reflux condenser. The temperature was maintained at 45° throughout. Acetic acid and 35% HCl was added dropwise until the solution went clear (approximately 10 ml of each). The mixture was then heated to 85°. After 45 minutes at this temperature the mixture was allowed to cool and the solution was filtered to remove the remaining iron powder. Slow addition of sodium carbonate to neutralize the acid, followed by extraction with with dichloromethane gave a residue that contained 2,3,4-trimethylaniline.[127] This was isolated by chromatography on a Chromatotron silica gel plate to give:

2,3,4-Trimethylaniline m.p. (pentane) 29-30° (Lit.[128] 24°) υ_{max} (KBr) 3400, NH2; 2940, methyl; 1620, 1485, 1269 cm-1 aromatic C=C. ^{1}H n.m.r. ($CDCl_3$) δ 2.10, s, 2-Me; 2.18, s, 3-Me; 2.20, s, 4-Me; 3.45, br s, NH_2; 6.49, d ($J_{H6,H5}$ 8.0 Hz), H6; 6.83, d ($J_{H5,H6}$ 8.0 Hz), H5. ^{13}C n.m.r. ($CDCl_3$) δ 13.19, 2-Me; 15.94, 3-Me; 20.26, 4-Me; 112.76, C6; 121.29, C1; 126.81, C2; 127.49, C5; 135.38, C3; 142.40, C4. λ_{max} ($CHCl_3$) 292, 241 nm (ε 2480, 7390).

Preparation of 2,3,4-Trimethylbiphenyl (92).

A mixture of fresh n-amylnitrite (10 g)[124] and 1,2,3-trimethylaniline (5 g) in benzene (200 ml) was heated until reaction occurred and this was allowed to proceed without further heating for 20 minutes. After this time the mixture was heated under reflux for a further three hours. The solvent was removed under reduced pressure to give an oil containing 2,3,4-trimethylbiphenyl (92).[126] Chromatography using a Chromatotron silica gel plate gave:

2,3,4-Trimethylbiphenyl (92) an oil at room temperature (Found C, 91.8 ; H, 8.2%. $C_{15}H_{16}$ requires C, 91.8; H, 8.2%). υ_{max} (liquid film) 3520, 2940, CH_3; 1605, 1476 cm^{-1}, aromatic C=C. ^{1}H n.m.r. ($CDCl_3$) δ 2.18, s, 2-Me; 2.25, s, 3-Me; 2.34, s,

4-Me; 7.00, d ($J_{H6,H5}$ 7.8 Hz), H6; 7.06, d ($J_{H5,H6}$ 7.8 Hz), H5; 7.2-7.6, five aromatic hydrogens. ^{13}C n.m.r. ($CDCl_3$) δ 15.97, 3-Me; 17.59, 2-Me; 20.76, 4-Me; 126.41, 127.00, 127.92, 128.72, 129.48; C5, C6, C1', C2', C3', C4', C5', C6'; 133.78, C4; 135.44, C3; 135.55, C5. λ_{max} ($CHCl_3$) 244 nm (ε 18600). N.O.e. results: irradiation of δ 2.18 gave a positive difference peak at δ 7.28 (2%) and irradiation at δ 2.34 gave positive difference peaks at δ 2.25 (1%) and δ 7.06 (4%).

Reaction of 2,3,4-Trimethylbiphenyl (92) with Nitrogen Dioxide in Benzene.

A solution of 2,3,4-trimethylbiphenyl (92) (500 mg) was treated with nitrogen dioxide, as above for two hours, to give an orange oil (779 mg), shown (^1H n.m.r.) to be a mixture (*c.*.1:1:trace:8:2:5:2:2:2) of 3,4-dimethyl-2-nitratomethylbiphenyl (111), 2,4-dimethyl-3-nitratomethylbiphenyl (112), 2,3-dimethyl-4-nitratomethylbiphenyl (113), 2,3,4-trimethyl-5-nitrobiphenyl (114), 2,3,4-trimethyl-4'-nitrobiphenyl (115), 2,3,4-trimethyl-6-nitrobiphenyl (116), 3,4,5-trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117), 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118), and unknown (119). This mixture was first separated into two fractions by normal phase HPLC using an Alltech CN 10 micron preparative HPLC column. The non-polar fraction was the fraction eluted by 20% dichloromethane in hexane and the polar fraction was the fraction eluted with dichloromethane.

Chromatography of the non-polar fraction on a Chromatotron silica gel plate at room temperature gave, in order of elution:

3,4-Dimethyl-2-nitratomethylbiphenyl (111) an oil. [Found M^++1 (methane C.I.) = 258.1128. $C_{12}H_{16}NO_3$ requires 258.1130]. υ_{max} (liquid film) 1630, 1290, 860 cm^{-1} nitrate. ^1H n.m.r. ($CDCl_3$) δ 2.19, s, 4-Me; 2.35, s, 3-Me; 5.54, s, CH_2ONO_2; 7.25, m, seven aromatic hydrogens. ^{13}C n.m.r. and λ_{max} could not be obtained. N.O.e. results: Irradiation at δ 2.19 gave positive difference peaks at δ 2.35 (2%) and δ 7.25 (1%). Irradiation at δ 2.35 gave positive difference peaks at δ 2.19 (2%) and δ 5.54 (2%). Irradiation at δ 5.54 gave a positive difference peak at δ 2.35 (1%).

2,4-Dimethyl-3-nitratomethylbiphenyl (112) was obtained only in admixture (1:1.2) with 2,3-dimethyl-4-nitratomethylbiphenyl (113). υ_{max} (liquid film) 1630, 1290,

860 cm^{-1} nitrate. ^1H n.m.r. ($CDCl_3$) δ 2.28, s, 2-Me; δ 2.46, s, 4-Me; 5.65, s, CH_2ONO_2; 7.20, m, aromatic hydrogens. N.O.e. results: Irradiation at δ 2.46 gave positive difference peaks at δ 5.65 (3%) and δ 7.20 (2%). Irradiation at δ 2.28 gave positive difference peaks at δ 5.65 (2%) and δ 7.20 (1%). Irradiation at δ 5.65 gave positive difference peaks at δ 2.26 (2%) and δ 2.46 (2%).

2,3-Dimethyl-4-nitratomethylbiphenyl (113) [Found M^+ (methane C.I.) = 257.1061. $C_{12}H_{15}NO_3$ requires 257.1061]. This compound was not isolated as a pure compound. υ_{max} (liquid film) 1630, 1280, 860 cm^{-1} nitrate. ^1H n.m.r. ($CDCl_3$) δ 2.35, s, Me; 2.36, s, Me; 5.39, s, CH_2ONO_2. N.O.e results: Irradiation at δ 5.39 gave positive difference peas at δ 2.35 (1%) and δ 7.30 (2%). With the line broadening the difference peak at δ 2.35 could be due to either or both of the methyl peaks.

2,3,4-Trimethyl-5-nitrobiphenyl (114) an oil [Found M^+ + 1 (isobutane C.I.) 242.1192 $C_{15}H_{16}NO_2$ requires 242.1181]. υ_{max} (liquid film) 2950, CH; 1720, C=C; 1523, 1358 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.23, s, 2-Me; 2.34, s, 3-Me; 2.44, s, 4-Me; 7.26, m, H2' and H6'; 7.41, m, H3', H4', H5'; 7.52, s, H6. ^{13}C n.m.r. ($CDCl_3$) δ 15.87, 2-Me; 16.77, 3-Me; 18.40, 4-Me; 122.44, 127.432, 128.32, C2', C3', C4', C5', C6'; 129.21, C6; 129.00, 130.36, 134.52, C2, C3, C4; 138.40, C1'; 139.40, C1'; 140.59, C5. λ_{max} ($CHCl_3$) 240 nm (ε 5700). N.O.e. results: Irradiation at δ 2.23 gave positive difference peaks at δ 2.34 (3 %) and δ 7.26 (3 %). Irradiation at δ 2.34 gave positive difference peaks at δ 2.23 (2 %) and δ 2.44 (2 %). Irradiation at δ 2.44 gave a positive difference peak at δ 2.34 (3 %). Irradiation at δ 7.52 gave a positive difference peak at δ 7.52 (2 %).

2,3,4-Trimethyl-4'-nitrobiphenyl (115) m.p. 114-117° [Found M^++1 (isobutane C.I.) 242.1192 $C_{15}H_{16}NO_2$ requires 242.1181]. υ_{max} (KBr) 1600, aromatic C=C; 1517, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.17, s, 2-Me; 2.26, s, 3-Me; 2.36, s, 4-Me; 6.97, d ($J_{H6,H5}$ 7.9 Hz), H6; 7.10, d ($J_{H5,H6}$ 7.9 Hz), H5; 7.45, d ($J_{H2',H3';H6',H5'}$ 8.8 Hz), H2' H6'; 8.26, d ($J_{H3',H2';H5',H6'}$ 8.8 Hz), H3', H5'. ^{13}C n.m.r. insufficient material. λ_{max} ($CHCl_3$) 308 nm (ε 3020). N.O.e. results: Irradiation at δ 2.17 gave a positive difference peak at δ 7.45 (1%). Irradiation at δ 2.36 gave a positive difference peak at δ 7.10 (14%). Irradiation at δ 7.10 gave a positive difference peak at δ 2.36. (1%).

Irradiation at δ 7.45 gave a positive difference peak at δ 2.17 (1%). Irradiation at δ 8.26 gave a positive difference peak at δ 7.45. (3%).

2,3,4-Trimethyl-6-nitrobiphenyl (116) m.p. 109-110° (Found C, 74.5; H, 6.2; N, 5.8 %. $C_{15}H_{15}NO_2$ required C, 74.7; H, 6.3; N, 5.8 %). υ_{max} (KBr) 2950, CH; 1510, 1330 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.03, s, 2-Me; 2.29, s, 3-Me; 2.40, s, 4-Me; 7.15, m, H2' and H6'; 7.40, m, H3', H4', H5'; 7.53, s, H5. ^{13}C n.m.r. ($CDCl_3$) δ 16.60, 3-Me; 17.90, 2-Me; 20.67, 4-Me; 122.04, C5'; 127.55, C5; 127.89, 128.66, 136.59, C2, C3, C4; 128.36, 128.82; C2', C3', C5', C6'; 137.14, C1'; 137.23, C1; 140.79, C6. λ_{max} ($CHCl_3$) 275 nm (ε 2400). N.O.e. results: Irradiation at δ 2.40 gave positive difference peaks at δ 2.29 (2 %) and δ 7.53 (9 %). Irradiation at δ 7.53 gave a positive difference peak at δ 2.40 (2 %). Irradiation at δ 7.15 gave positive difference peaks at δ 2.03 (1 %) and δ 7.40 (5 %).

Separation of the more polar fraction from the H.P.L.C., above, using a Chromatotron silica gel plate at low temperature gave impure samples of three compounds present in the original product mixture:

The first, 3,4,5-trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117), gave the following spectroscopic data: υ_{max} (liquid film) 1650, C=O; 1550, 1350, 750 cm^{-1}, nitro. ^1H n.m.r. ($CDCl_3$) δ 1.81, s, Me; 1.97, s, Me; 2.03, d ($J_{4\text{-Me, H}}$ 1.5 Hz), 4-Me; 6.35, q ($J_{H,4\text{-Me}}$ 1.5 Hz), H; 7.13, m, two aromatic hydrogens; 7.42, m, three aromatic hydrogens. N.O.e. irradiation at δ 2.03 gave a positive difference peak at δ 6.35 (8%). This compound (117) was only obtained in admixture (*c.* 2:1) with 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118), below.

The second compound, 3,4,5-trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118), gave the following spectroscopic data: υ_{max} (liquid film) 1670, C=O; 1550, 1380 cm^{-1}, nitro. ^1H n.m.r. ($CDCl_3$) δ 1.89, s, Me; 2.07, s, Me; 2.08, s, Me; 7.13, m, 7.42, m, aromatic hydrogens. This compound rearranged on storage in $CDCl_3$ to give 3,4,5-trimethyl-2-nitro-4-hydroxy-6-phenylcyclohexa-2,5-dienone (120); see below.

The third compound, unknown (119), was obtained only in admixture (1:2) with 3,4,5-trimethyl-4-nitro-2-phenylcyclohexa-2,5-dienone (117). ^1H n.m.r. δ ($CDCl_3$) 1.90, s, Me; 2.03, s, Me; 2.07, d (J 1.1 Hz), Me·

Rearrangement of 3,4,5-Trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118) in (D)-Chloroform to give 4-Hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120):

Storage of 3,4,5-Trimethyl-2,4-dinitro-6-phenylcyclohexa-2,5-dienone (118) (8 mg) in (D)-Chloroform (0.75 ml) at 24° for one week gave:

4-Hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120): m.p. 197-199° (Single crystal X-ray structure analysis: see Appendix A). υ_{max} (KBr) 3420, OH; 2950, 1450 Me; 1681, free C=O; 1640, H-bonded C=O; 1540, 1390, 738 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.65, s, Me; 2.02, s, Me; 2.19, s, Me; 7.08, m, H2' H3'; 7.39, m, H3' H4' H5'. ^{13}C n.m.r. and λ_{max} insufficient material.

Attempted Reaction of 2,3,4-Trimethyl-5-nitrobiphenyl (114) with Nitrogen Dioxide in Benzene.

A solution of 2,3,4-trimethyl-5-nitrobiphenyl (114) (45 mg) was treated with nitrogen dioxide, as above for two hours, to give an orange oil (48 mg), shown (^1H n.m.r.) to be unchanged 2,3,4-trimethyl-5-nitrobiphenyl (114).

Attempted Reaction of 2,3,4-Trimethyl-6-nitrobiphenyl (116) with Nitrogen Dioxide in Benzene.

A solution of 2,3,4-trimethyl-6-nitrobiphenyl (116) (45 mg) was treated with nitrogen dioxide, as above for two hours, to give an orange oil (48 mg), shown (^1H n.m.r.) to be unchanged 2,3,4-trimethyl-6-nitrobiphenyl (116).

5.4 Experimental To Chapter 4.

5.4.1 Reaction of Phenanthrene (130) with Nitrogen Dioxide in Benzene.

Treatment of a solution of phenanthrene (130) (500 mg) with nitrogen dioxide, as above, for two hours gave a yellow solid (817 mg), shown (^1H n.m.r.) to be a mixture (*c.* 1.5:4.6:1:1.1:3.3:1) of dimeric nitro nitrate (132), 9-nitrophenanthrene (131),

3-nitrophenanthrene (133), 1-nitrophenanthrene (134), *trans*- nitro nitrate (135), and *cis*- nitro nitrate (136).

Filtration of the reaction mixture gave a colourless solid : 10-Nitro-9,9',10,10'-tetrahydro-9,9'biphenanthren-10-yl nitrate (132) m.p. 153-154° (Lit.[114] 156-158°) υ_{max} (KBr) 1620, 1251, 732 nitrate, 1550, 1335 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 2.98, d of d ($J_{H9',H9}$ 12 Hz; $J_{H9',H10'}$ 2.5 Hz), H9'; 3.51, d of d ($J_{H9,H9'}$ 11 Hz, $J_{H9,H10}$ 2.3 Hz), H9; 5.25, d ($J_{H10,H9}$ 2.2 Hz), H10; 5.76, d ($J_{H10',H9'}$ 2.3 Hz), H10'; 6.87, d of d ($J_{H8',H7'}$ 7.4 Hz, $J_{H8',H6'}$ 1.5 Hz), H8'; 6.96, d of d ($J_{H8,H7}$ 6.3 Hz, $J_{H7,H6}$ 1.5 Hz), H8; 7.36, m, H7, H7'; 7.45, m, H1, H2, H6, H1', H2', H6'; 7.66, m, H3, H3', 7.87, d (JH5',H6' 7.9 Hz), H5'; 7.90, d ($J_{H5,H6}$ 7.1 Hz), H5; 7.98, d ($J_{H4',H3'}$ 7.0 Hz), H4'; 8.00, d ($J_{H4,H3}$ 6.6 Hz), H4. ^{13}C n.m.r. ($CDCl_3$) could not be obtained. λ_{max} ($CHCl_3$) 271, 240 nm (ε 24500, 17400). N.O.e. results: irradiate δ 2.98 peak enhancements at: δ 5.76 (14%), δ 6.87 (11%). Irradiate δ 3.51 peak enhancements at: δ 5.25 (10%), δ 6.96 (11%). Irradiate δ 5.25 peak enhancements at: δ 3.51 (10%), δ 6.87 (7%). Irradiate δ 5.76 peak enhancements at: δ 2.98 (6%), δ 6.96 (6%). Irradiate δ 6.87 peak enhancements at: δ 2.98 (11%), δ 5.25 (6%), δ 7.36 (5%). Irradiate δ 6.96 peak enhancements at: δ 3.51 (12%), δ 5.76 (6%), δ 7.36 (6%). Irradiate δ 7.87 peak enhancements at: δ 7.45 (7%), δ 7.98 (7%). Irradiate δ 8.00 peak enhancements at: δ 7.66 (10%), δ 7.90 (9%). Reported analytical data: Schmit, J.[110] m. p. 154-155°. Heaney H., Jones A. J. and Miller I. T[114] m. p. 156-158° [recrystallisation from anhydrous acetone gave material m. p. 161-163° (dec.)] (Found: C, 72.3; H, 4.75; N, 6.05%. $C_{28}H_{20}N_2O_5$ requires C, 72.4; H, 4.35; N, 6.05%). υ_{max} 1620, 1280, 870 cm^{-1} nitrate; 1545, 1360 cm^{-1} nitro. λ_{max} ($CHCl_3$) 271 nm (ε 30200). Cohen, D. *et. al.*[112] ^1H n.m.r. (a saturated solution in $CDCl_3$) δ 3.52, d of d ($J_{H9',H9}$ 11.2 Hz; $J_{H9',H10'}$ 2.1 Hz), H9'; 5.76, d of d ($J_{H9,H9'}$ 11.2 Hz, $J_{H9,H10}$ 2.1 Hz), H9; 6.90, m, relative area 2 hydrogens; 7.43, m, relative area 10 hydrogens; 7.90, m, relative area 4 hydrogens.

The three nitrophenanthrenes, (131), (133) and (134), were isolated by chromatography using a Chromatotron silica gel plate and pentane as the eluting solvent:

9-Nitrophenanthrene (131) m.p. 114-115° (Lit.[86] 116-117°). υ_{max} (KBr) 1511, 1450 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 7.71, m, H2, H3, H6, H7; 7.96, d ($J_{H1,H2}$ 8.5 Hz), H1; 8.42, s, H10; 8.44, m, H4 or H5; 8.65, d ($J_{H8,H7}$ 8.1 Hz), H8; 8.71, m, H4 or H5. ^{13}C n.m.r. ($CDCl_3$) δ could not be obtained. λ_{max} ($CHCl_3$) 250, 346 nm (ε 15700, 2160). N.O.e. results: Irradiate δ 7.71 peak enhancements at: δ 7.96 (5%), δ 8.44 (8%), δ 8.65 (7%) and δ 8.71 (11%). Irradiate δ 7.96 peak enhancements at: δ 7.71 (6%), and δ 8.42 (8%). Irradiate δ 8.42 peak enhancement at: δ 7.96 (3%). Irradiate δ 8.65 peak enhancements at: δ 7.71 (6%).

3-Nitrophenanthrene (133) m.p. 175.5-176° (Lit.[86] 170-171°). υ_{max} (KBr) 1603, 1335 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 7.77, m, H6; 7.83, m, H7, H10; 7.90, m, H8, H9; 8.02, d ($J_{H1,H2}$ 8.7 Hz), H1; 8.40, d of d ($J_{H2,H1}$ 8.5 Hz, $J_{H2,H4}$ 2.2 Hz), H2; 8.77, d ($J_{H5,H6}$ 8.5 Hz), H5; 9.62, d ($J_{H4,H2}$ 2.3 Hz), H4. ^{13}C n.m.r. ($CDCl_3$) δ could not be obtained. λ_{max} ($CHCl_3$) 247, 344 nm (ε 60000, 13600). N.O.e. results: Irradiate δ 8.40 peak enhancement at: δ 8.02 (8%). Irradiate δ 8.77 peak enhancements at: δ 7.77 (5%), δ 9.62 (23%). Irradiate δ 9.62 peak enhancements at: δ 8.77 (19%).

1-Nitrophenantherene (134) m.p. 131-132° (Lit.[117] 133-134°.) υ_{max} (KBr) 1605, aromatic C=C; 1520, 1340 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 7.71, m, H3, H6, H7; 7.95, d ($J_{H2,H3}$ and $J_{H10,H9}$ 9.5 Hz), H2 and H10; 8.18, m, H8; 8.30, d, ($J_{H9,H10}$ 9.2 Hz), H9; 8.68, br d ($J_{H5,H6}$ 7.7 Hz); H5; 8.97, d ($J_{H4,H3}$ 8.5 Hz), H4. ^{13}C n.m.r. ($CDCl_3$) δ could not be obtained. λ_{max} ($CHCl_3$) 248, 350 nm (ε 3680, 350). N.O.e. results: Irradiate δ 7.71 peak enhancements at: δ 7.95 (4%), δ 8.18 (4%), δ 8.68 (4%) and δ 8.97 (3%). Irradiate δ 7.95 peak enhancements at: δ 7.71 (1%), δ 8.30 (5%). Irradiate δ 8.18 peak enhancement at: δ 7.71 (1%). Irradiate δ 8.30 peak enhancement at: δ 7.95 (5%). Irradiate δ 8.68 peak enhancements at: δ 7.71 (2%), δ 8.97 (8%). Irradiate δ 8.97 peak enhancements at: δ 7.71 (7%), δ 8.68 (10%).

The remaining two compounds: the *trans-* and *cis-* nitronitrates (135), (136) decomposed on the Chromatotron silica gel plate and were finally isolated using an Ecosil cyanopropyl column in normal phase H.P.L.C.

Trans-*10-nitro-9,10-dihydrophenthrene-9-yl nitrate* (135) m.p. 95-96° (Single Crystal X-ray structure determination see Appendix A). υ_{max} (KBr) 1618, 1254, 835 nitrate, 1546 1345 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 5.84, d ($J_{H10,H9}$ 3.4 Hz), H10; 6.73, d ($J_{H9,H10}$ 3.4 Hz), H9; 7.39-7.62, m, H1, H2, H3, H6, H7, and H8; 7.90, m, H4, H5. ^{13}C n.m.r. could not be obtained because the material was unstable. λ_{max} ($CHCl_3$) 275 nm (ε 6550). N.O.e. results: Irradiate δ 5.84 peak enhancements at: δ 6.73 (9%), δ 7.46 (5%). Irradiate δ 6.73 peak enhancements at: δ 5.84 (7%), δ 7.53 (8%).

Cis--10-nitro-9,10-dihydrophenthrene-9-yl nitrate (136) was only obtained in admixture (approximately 9:1) with the *trans-* isomer (135). υ_{max} (liq. film) 1658, 1288, 840 nitrate, 1520, 1368 cm^{-1} nitro. ^1H n.m.r. ($CDCl_3$) δ 5.98, d, ($J_{H10,H9}$ 4.8 Hz), H10; 6.58, d ($J_{H9,H10}$ 4.8 Hz), H9; 7.38-7.62, m, H1, H2, H3, H6, H7, H8; 7.90, m, H4, H5. N.O.e. results: Irradiate δ 5.98 peak enhancements at: δ 6.58 (12%), δ 7.49 (7%). Irradiate δ 6.58 peak enhancement at: δ 5.98 (13%).

Reaction of a Concentrated Solution of Phenanthrene (130) with Nitrogen Dioxide in Benzene.

Treatment of a concentrated solution of phenanthrene (130) (1 g) in dry benzene (4 ml) as above for two hours gave a yellow solid (1.8 g), shown (^1H n.m.r.) to be a mixture (*c.* 2.5:3.6:1:1.6:2.8:1.1) of dimeric nitro nitrate (132), 9-nitrophenanthrene (131), 3-nitrophenanthrene (133), 1-nitrophenanthrene (134), *trans-* nitro nitrate (135), and *cis-* nitro nitrate (136).

Reaction of a Dilute Phenanthrene (130) Solution with Nitrogen Dioxide in Benzene.

Treatment of a dilute solution of phenanthrene (130) (50 mg) in dry benzene (5 ml), as above gave a yellow oil (130 mg), shown (^1H n.m.r.) to be a mixture (*c.* trace:2.8:1.3:1.8:5.1:1) of dimeric nitro nitrate (132), 9-nitrophenanthrene (131),

3-nitrophenanthrene (133), 1-nitrophenanthrene (134), *trans*- nitro nitrate (135), and *cis*- nitro nitrate (136).

5.4.2 Gas Chromatography of Phenanthrene Products and Product Mixtures.

A Shimadzu GC-9AM gas chromatograph equipped with a flame ionization detector operated isothermally at 235° was used for these analyses; a preliminary investigation had shown that isothermal operation at this temperature gave good separation of the nitrophenanthrene isomers. The injector and the detector ports were set at 260° and the carrier gas (Helium) flow rate was approximately 6 ml. min^{-1}. The effluent/split ratio was approximately 40:1. Two capillary columns were used, a DB1301 and a DB17. Each capillary column had an internal diameter of 0.5 mm, with a film thickness of 1 μm and was 15 m long. No differences in retention times were observed between the two columns. 1 μl injections of the sample (1 mg ml^{-1} in chloroform) were injected into the injector port manually. Prepared solutions were stored in iced water prior to injection to prevent any decomposition in solution. Four standards were used: three contained 1 mg of purified nitrophenanthrene (131), (133) or (134) and the fourth contained known amounts of all three nitrophenanthrenes. In addition to this, a pure phenanthrene (130) and a pure benzene standard was also injected. Benzene, the reaction solvent, is eluted with the solvent front and does not give an extra peak. The response factors found for the three nitrophenanthrene isomers and the phenanthrene are similar, so direct comparison is possible. The Gas Chromatography-Mass Spectrometry was run using the following instrument: HP5970B Mass Selective Detector, HO5890 Gas Chromatograph, and a HP59940 Chem. Station. The column was an Ultra2 (25m x 0.2 mm x 0.11 μm).

Gas Chromatography of 10-Nitro-9,9',10,10'-tetrahydro-9,9'biphenanthren-10-yl nitrate (132).

Injection of a 1 mg ml-1 solution of the dimeric nitro nitrate (132) onto a DB1301 capillary column gave three peaks with retention times corresponding to phenanthrene

(130) (68%), unknown (151) (4%), and 9-nitrophenanthrene (131) (37%). G.C./M.S. confirmed that the peak at retention time 2.19 minutes was phenanthrene (130) and that the peak at retention time 7.57 minutes was 9-nitrophenanthrene (131); the third peak was not be detected.

Gas Chromatography of Trans-*10-nitro-9,10-dihydrophenthrene-9-yl nitrate(135).*

Injection of a 1 mg ml^{-1} solution of the *trans* -nitro nitrate (135) onto a DB17 capillary column gave a trace with eight peaks. Four of these compounds are present in minor amounts (< 5%); only phenanthrene (130) (retention time 2.2 minutes) could be identified from this group. Two unidentified compounds were present in significant amounts: The first (unknown 149) (8.8%), retention time 2.8 minutes, was not a pyrolysis product of the dimer nitro nitrate (132). The second unknown compound [unknown (151) (19.1%], retention time 5.9 minutes) was also a pyrolysis product of the dimer nitro nitrate (132). The only identifiable major pyrolysis product was 9-nitro-phenanthrene (131), (retention time of 7.6 minutes) which accounted for 59.7% of the observed material.

G.L.C. Analysis of the Products of the Normal Phenanthrene/Nitrogen Dioxide Reaction (DB1301).

Reaction of phenanthrene (130) (500 mg) in benzene (5 ml), as above, gave a mixture of products (^1H n.m.r.): dimeric nitro nitrate (132) (12%), 9-nitrophenanthrene (131) (37%), 3-nitrophenanthrene (133) (8%), 1-nitrophenanthrene (134) (9%), *trans*-nitronitrate (135) (26%), and *cis*- nitronitrate (136) (8%). These were injected onto the column to give a G.C. trace with significant amounts of phenanthrene (130), and unknown (151), in addition to the three nitrophenanthrene isomers (131), (133) and (134). The presence of phenanthrene (130) and the greatly increased proportion of 9-nitro-phenanthrene (131) is especially noteworthy.

G.L.C. Analysis of the Products of the Concentrated Phenanthrene Solution/Nitrogen Dioxide Reaction (DB1301).

Reaction of phenanthrene (130) (1 g) in benzene (4 ml), as above, gave a mixture of products (^{1}H n.m.r.): dimeric nitro nitrate (132) (20%), 9-nitrophenanthrene (131) (29%), 3-nitrophenanthrene (133) (8%), 1-nitrophenanthrene (134) (13%), *trans*- nitro nitrate (135) (22%), and *cis*- nitro nitrate (136) (9%). This mixture was injected onto the G.C., giving the data summarized in Table 5.4; below.

G.L.C. Analysis of the Products of the Dilute Phenanthrene Solution/Nitrogen Dioxide Reaction (DB1301).

Reaction of phenanthrene (130) (50 mg) in benzene (5 ml), as above, gave a mixture of compounds (^{1}H n.m.r.): dimeric nitro nitrate (132) (trace), 9-nitro-phenanthrene (131) (23%), 3-nitrophenanthrene (133) (11%), 1-nitrophenanthrene (134) (15%), *trans*- nitro nitrate (135) (43%), and *cis*- nitro nitrate (136) (8%). These were injected onto the G.C.; giving data summarized in Table 5.5; below.

Analysis of this mixture by GCMS confirmed the identity of the three peaks, 9-, 1- and 3- nitrophenanthrene (131), (134) and (133) above. Unknown (151) gave a mass spectrum containing peaks at m/e 210, 181, 165, 153, 152 and 76, but its identity remains uncertain.

Table 5.1: **Pyrolysis products of the Dimeric Nitro Nitrate (132) on the DB1301 Column.**

Retention Time	Average Area (%)	
2.19	59.01	phenanthrene (130).
5.89	4.00	unknown (151).
7.57	36.99	9-nitrophenanthrene (131).
	100.00	

Table 5.2: **Pyrolysis products of the *Trans* -nitro nitrate (135) on a DB17 column.**

Retention Time.	Area Compound (%)	
1.99	2.48	unknown (147)
2.20	2.00	phenanthrene (130)
2.61	2.29	unknown (148)
2.78	8.81	unknown (149)
3.74	1.11	unknown (150)
5.89	19.06	unknown (151)
7.58	59.67	9-nitrophenanthrene (131).
7.80	4.58	
	100%	

Table 5.3: **G.L.C. Analysis of a Product Mixture from the Normal Phenanthrene/Nitrogen Dioxide Reaction (DB1301).**

Retention Time (minutes)	Average(%)	
2.17	4.08	phenanthrene (130).
2.61	0.14	unknown (148)
2.79	0.60	unknown (149)
3.90	0.32	unknown (150)
5.82	8.53	unknown (151)
7.48	63.00	9-nitrophenanthrene (131)
7.92	12.34	1-nitrophenanthrene (134)
8.29	10.98	3-nitrophenanthrene (133)
	100.00	

Table 5.4: **G.L.C. Analysis of the Products of the Concentrated Phenanthrene Solution/Nitrogen Dioxide Reaction (DB1301).**

Retention Time (minutes)	Average (%)	
2.20	1.16	phenanthrene (130).
2.79	0.29	unknown (149)
3.90	0.28	unknown (150)
5.84	7.33	unknown (151)
7.51	65.42	9-nitrophenanthrene (130).
7.96	13.85	1-nitrophenanthrene (134).
8.33	11.68	3-nitrophenanthrene (133).
	100.00	

Table 5.5: **G.L.C. Analysis of the Products of the Dilute Phenanthrene Solution/Nitrogen Dioxide Reaction (DB1301).**

Retention Time (minutes)	Average (%)	
2.19	0.64	phenanthrene (130).
2.59	0.21	unknown (148)
2.77	0.92	unknown (149).
3.89	0.17	unknown (150)
5.86	13.46	unknown (151).
7.53	57.35	9-nitrophenanthrene (131).
7.98	14.14	1-nitrophenanthrene (134).
8.36	13.11	3-nitrophenanthrene (133).
	100.00	

5.5 Experimental To Appendix B.

5.5.1 Preparation and Reaction with Nitrogen Dioxide of Compounds in the 3,4,5-Trimethylbenzene Derivatives.

Preparation of 1,2,3-Trimethyl-5-nitrobenzene (153) and 1,2,3-Trimethyl-4-nitrobenzene (154).

A mixture of nitric acid (density 1.42 gm ml^{-1}, 19.7 ml) and sulphuric acid (density 1.8 gm ml^{-1}, 21.1 ml) was added dropwise (2.5 hours) to a stirred quantity of 1,2,3-trimethylbenzene (40 ml) in a 250 ml three-necked round bottomed flask. The temperature was maintained between 0-8° throughout this addition. After this time the mixture was stored at room temperature for a further three hours.

The mixture was then poured into crushed ice (400 ml) in a 1 l separating funnel and was extracted with dichloromethane (3 x 200 ml). The dichloromethane extracts were combined into a 1 l separating funnel and were washed with water, 10% aqueous sodium hydroxide, dried over magnesium sulphate and distiled through a 10 inch Nester-Faust spinning band column. The initial fractions containing 1,2,3-trimethyl-4-nitrobenzene (154) in admixture with 1,2,3-trimethyl-5-nitrobenzene (153) were combined and re-distiled to give the 1,2,3-trimethyl-4-nitrobenzene (154) used in the preparation of 2,3,4-trimethylbiphenyl (92), above.

The later fractions, which crystalized on cooling, and the still-pot residue were combined and recrystallised from petroleum ether and then from methanol to give: 1,2,3-trimethyl-5-nitrobenzene (153) (yield 10%) m.p. 66-67° (Lit.[129] 65-66°). υ_{max} (Nujol) 1520, 1350 cm^{-1}, nitro. ^1H n.m.r. ($CDCl_3$) δ 2.24, s, 4-Me; 2.35, s, 3- 5- methyls; 7.82, s, H2, H6. ^{13}C n.m.r. ($CDCl_3$) δ 15.85, 4–Me; 20.55, 3-, 5- methyls; 122.02, C2, C6; 137.75, C3, C5; 143.20, C4; 145.27, C1. λ_{max} ($CHCl_3$) 236, 288 nm (ε 1300, 6949).

Preparation of 3,4,5-Trimethylphenylacetate (155).

Acetic anhydride (23 ml) was added to a mixture of 3,4,5-trimethylphenol (58) (15 g) in sodium hydroxide solution (3 mole l^{-1}, 75 ml) and crushed ice. The mixture was

then shaken vigorously for 2 minutes. The acetate separated as a colourless solid that was collected and recrystallised from hot petroleum ether to give:

3,4,5-Trimethylphenylacetate (155) yield 95%: m.p. 56-57° (Lit.[130] 59°) υ_{max} (Nujol) 1754, carbonyl; 1600 cm^{-1}, C=C. ^1H n.m.r. ($CDCl_3$) δ 2.08, s, 4-Me; 2.22, s, 3-, 5- methyls, OAc; 6.69, s, H2, H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.82, 4–Me; 20.51, 3- 5- Me; 20.94, acetate methyl; 132.58, C2, C6; 137.56, C3, C5; 142.55, C1; 147.79, C4; 169.85, C=O. λ_{max} ($CHCl_3$) 240, 270 nm (ε 940 370)

Preparation of 1-Bromo-3,4,5-trimethylbenzene (156).

3,4,5-Trimethylaniline (157) (100 g) was added to a stirred solution of freshly prepared n-amyl nitrite[124] in bromoform (400 ml). After storage at 100° for one hour the bromoform was removed under reduced pressure to give a residue which gave pure 1-bromo-3,4,5-trimethylbenzene (156) upon chromatography off a Chromatotron silica gel plate.

1-Bromo-3,4,5-trimethylbenzene (156) yield 18%: A colourless oil (Lit.[131]). υ_{max} (Nujol) 2970, CH; 1575, C=C; 1165 cm^{-1}, CBr. ^1H n.m.r. ($CDCl_3$) δ 2.09, s, 4-Me; 2.23, s, 3-, 5- methyls; 7.13, s, H2, H6. ^{13}C n.m.r. ($CDCl_3$) δ 15.01, 4–Me; 20.32, 3- 4- Me; 118.47, C1; 130.11, C2, C6; 133.92, C3, C5; 138.46, C4. λ_{max} ($CHCl_3$) 240 nm (ε 1530)

Preparation of 1-Cyanio-3,4,5-trimethylbenzene (158).

3,4,5-Trimethylaniline (157) (5 g) was dissolved in a mixture of conc hydrochloric acid (10 ml) and ice (40 g), addition of 30% sodium nitrite solution until starch paper indicated the presence of nitrous acid. The solution was then neutralized with sodium carbonate. The temperature was kept below 0° throughout this preparation.

The diazonium solution, prepared above, was then added slowly to a cold solution of cuprous cyanide (4.5 g) in water (30 ml).[132] This solution was stirred rapidly and was covered with a layer of toluene (20 ml). Reaction was at room temperature (2 h) and then at 50° (2 h). The toluene layer was decanted off, dried over magnesium sulphate and the solvent was removed to give a residue containing 1-cyanio-3,4,5-trimethylbenzene

(158). Chromatography using a Chromatotron silica gel plate followed by recrystallisation from petroleum ether gave:

1-Cyanio-3,4,5-trimethylbenzene (158) (yield 60%) mp 93-95° (Lit.[131] 96.5-97.5°). υ_{max} (KBr) 2900, C-H; 2230, CN; 1550 cm^{-1}, aromatic C=C. ^1H n.m.r. ($CDCl_3$) δ 2.22, s, 4-Me; 2.30, s, 3-, 5- Methyls; 7.27, s, H2, H6. ^{13}C n.m.r. ($CDCl_3$) δ 15.80, 4-Me; 20.37, 3-, 5- methyls; 119.41, CN; 130.80, C2, C6; 134.49, C4; 137.61, C3, C5; 141.11, C1. λ_{max} ($CHCl_3$) 244, 277, 350 (ε 13400, 1500, 610).

Preparation of 5-t -Butyl-1,2,3-trimethylbenzene (159).

5-*t* -Butyl-1,2,3-trimethylbenzene (159) was prepared by condensation of *t* -butanol with 1,2,3-trimethylbenzene in the presence of aluminium chloride. The method used was adapted from that described by Norris and Sturgis.[133]

A cooled solution of *t* -butanol (28 ml) dissolved in 1,2,3-trimethylbenzene (200 ml) was added to aluminium chloride (120 g) in an ice/salt bath. The mixture was then stirred with a mechanical stirrer for 5 h. After this time the mixture was poured into iced water and the organic fraction was extracted into petroleum ether, was dried over $MgSO_4$, and the petroleum ether was removed under reduced pressure. The residual liquid, a mixture of 1,2,3-trimethylbenzene and 5-*t* -butyl-1,2,3-trimethylbenzene (159), was distiled under nitrogen to remove the majority of the 1,2,3-trimethylbenzene. Pure 5-*t* -butyl-1,2,3-trimethylbenzene (159) (7.7 g, 15%) was then obtained by vacuum distillation.

5-*t* -Butyl-1,2,3-trimethylbenzene (159) m.p. 29-30.5° (Lit.[134, 135] 30-32°). υ_{max} (thin film) 2890 cm^{-1}, C-H. ^1H n.m.r. ($CDCl_3$) δ 1.29, s, *t* -butyl; 2.14, s, 2-methyl; 2.28, s, 1- and 3- methyls; 7.03, s, H4, H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.97, 4-Me; 20.82, 3-, 5- methyls; 31.42, $C(\underline{C}H_3)_3$; 34.08, $\underline{C}(CH_3)_3$. λ_{max} ($CHCl_3$) 238, 266 nm (ε 745, 230).

The Reaction of 5-t -Butyl-1,2,3-trimethylbenzene (159) with Nitrogen Dioxide in Benzene at 5°.

Treatment of solution of 5-*t* -butyl-1,2,3-trimethylbenzene (159) (500 mg) in dry benzene (5 ml), as above for 2 h, gave a yellow oil (689 mg), shown to be a mixture containing unreacted substrate (35%). Therefore, the reaction time was extended to 9 h. This second experiment gave an orange oil shown (^{1}H n.m.r.) to contain some 12 compounds. Three of these compounds were isolated by chromatography using a Chromatotron silica gel plate; see below. These three compounds account for 63% of the *t* -butyl integral present in the original ^{1}H n.m.r. spectrum. The remaining compounds could not be isolated because they either decomposed or they were present as components of inseparable mixtures.

Chromatography on a Chromatotron silica gel plate gave in order of elution (The number in brackets is the estimated amount present in the original product mixture by analysis of the ^{1}H n.m.r. spectrum):

t -Butyl-4,5-dimethyl-3-nitromethylbenzene (160) (13%) m.p. 77.5-78.5 (Lit.[135] 77-78). υ_{max} (KBr) 1540, 1345 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.31, s, *t* -butyl; 2.25, s, 4-Me; 2.32, s, 5-Me; 5.51, s, nitromethyl; 7.19, d ($J_{H2,H6}$ 2 Hz), H2; 7.271, d ($J_{H6,H2}$ 2 Hz), H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.94, 4-Me; 20.83, 5-Me; 31.26, $C(\underline{C}H_3)_3$, 34.25; $\underline{C}(CH_3)_3$; 78.67, nitromethyl; 126.41, C2; 127.99, C3; 129.18, C6; 133.78, C4; 137.41, C5; 148.98, C1. λ_{max} ($CHCl_3$) 279 nm (ε 1380). N.O.e. results: Irradiation at δ 2.25 gave a positive difference peak δ 5.51 (3%). Irradiation at δ 2.32 gave a positive difference peak at δ 7.27 (2%). Irradiation at δ 5.51 gave positive difference peaks at δ 2.25 (3%) and δ 7.19 (12%).

5-*t* -Butyl-1,2,3-trimethyl-4-nitrobenzene (161) (41%) m.p. 71-72° (Lit.[135] 89-91°). υ_{max} (KBr) 1540, 1351 cm^{-1} NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.35, s, *t* -butyl; 2.11, s, 2-Me; 2.18, s, 1-Me; 2.31, s, 3-Me; 7.15, s, H. ^{13}C n.m.r. ($CDCl_3$) δ 14.81, 2-Me; 15.77, 3-Me; 21.04, 1-Me; 30.91, $C(\underline{C}H_3)_3$; 35.20, $\underline{C}(CH_3)_3$; 126.87, C6; 127.65, C3; 134.49, C2; 136.54, C4; 149.85, C4. λ_{max} ($CHCl_3$) 213, 260 nm (ε 166, 345).

5-t -Butyl-2-methyl-3,5-dinitromethylbenzene (162) (5%) m.p. 116-117.5°. (Found: C, 58.6; H, 6.9; N, 10.5%. $C_{13}H_{18}N_2O_4$ requires C, 58.6; H, 6.8; N, 10.5). υ_{max} (KBr) 1544, 1350 cm^{-1}; NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.33, s, *t* -butyl; 2.39, s, Me; 5.55, s, nitromethyl; 7.46, s, H2, H6. ^{13}C n.m.r. ($CDCl_3$) δ 14.77, Me; 31.11, $C(\underline{C}H_3)_3$; 34.49, $\underline{C}(CH_3)_3$; 78.14, nitromethyl; 129.38, C1, C3; 130.94, C4, C6; 135.65, C2; 150.27, C5. λ_{max} ($CHCl_3$) 238, 282 nm (ε 1129, 1610).

Attempted Reaction of t-*Butyl-4,5-dimethyl-3-nitromethylbenzene (161)with Nitrogen Dioxide in Benzene..*

Treatment of a solution of *t* -butyl-4,5-dimethyl-3-nitromethylbenzene (161) (100 mg) in dry benzene (1 ml) as above for two hours gave a yellow solid (70 mg), shown (^1H n.m.r.) to be essentially pure substrate with only traces of other compounds present.

Attempted Reaction of 5-t-Butyl-1,2,3 trimethyl-4-nitrobenzene (161) with Nitrogen Dioxide in Benzene..

Treatment of a solution of 5-*t* -butyl-1,2,3 trimethyl-4-nitrobenzene (161) (100 mg) in dry benzene (1 ml) as above for two hours gave a solid (150 mg), shown (^1H n.m.r.) to be essentially pure substrate (161).

Attempted Reaction of 3,4,5-Trimethylnitrile (158) with Nitrogen Dioxide in Benzene.

Treatment of a solution of 3,4,5-trimethylnitrile (158) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (594 mg), shown (^1H n.m.r.) to be essentially pure substrate (158).

Attempted Reaction of 1,2,3-Trimethyl-5-nitrobenzene (153) with Nitrogen Dioxide in Benzene.

Treatment of a solution of 1,2,3-trimethyl-5-nitrobenzene (153) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (486 mg), shown (^1H n.m.r.) to be essentially unchanged 1,2,3-trimethyl-5-nitrobenzene (153).

Attempted Reaction of 3,4,5-Trimethylphenylacetate (155) with Nitrogen Dioxide in Benzene.

Treatment of a solution of 3,4,5-trimethylphenylacetate (155) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (531 mg), shown (^{1}H n.m.r.) to be essentially pure substrate (155).

Attempted Reaction of 5-Bromo-1,2,3-trimethylbenzene (156) with Nitrogen Dioxide in Benzene.

Treatment of a solution of 5-bromo-1,2,3-trimethylbenzene (156) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (515 mg), shown (^{1}H n.m.r.) to be essentially pure substrate (156).

Attempted Reaction of Biphenyl (107) with Nitrogen Dioxide in Benzene.

Treatment of a solution of biphenyl (107) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (523 mg), shown (^{1}H n.m.r.) to be essentially pure substrate (107).

Attempted Reaction of 1,2,3-Trimethylbenzene (163) with Nitrogen Dioxide in Benzene.

Treatment of a solution of 1,2,3-trimethylbenzene (163) (500 mg) in dry benzene (5 ml) as above for two hours gave a solid (308 mg), shown (^{1}H n.m.r.) to be essentially pure substrate (163).

Appendix (A)

Crystallography.

Crystallography; 3,4,5-Trimethyl-4'-nitrobiphenyl (98). Crystal unit cell data were measured accurately using a Nicolet XRD P3 four-circle diffractometer and are given below. The space group was determined unambiguously from the systematic absences (h00, h=2n+1; 0k0, k=2n+1; 00l, l=2n+1).

Molybdenum X-radiation from a crystal monochrometer [λ(MoKα) 0.71069 Å] and the ω scan technique were used to collect reflection intensities at 183 K out to a maximum Bragg angle θ 26°.

The cell parameters were determined by least-squares refinement using the setting angles of 25 accurately centred reflections ($28° \leq 2\theta \leq 30°$). Absorption corrections were not applied.

Crystal Data:

3,4,5-Trimethyl-4'-nitrobiphenyl (98). $C_{15}H_{15}NO_2$, *M* 238.277, orthorhombic, space group $P\,2_12_12_1$, *a* 7.242(2), *b* 14.397(6), *c* 12.047(6) Å, *U* 1256 Å^3, D_m 1.24 g cm^{-3}, D_c 1.26 g cm^{-3}, Z 4, μ(Mo Kα) 0.89 cm^{-1}. The crystal was colourless and of approximate dimensions 0.1 by 0.1 by 0.4 mm. Number of independent reflections measured 1457, number with $I > 2\sigma(I)$ 765; *g* 0.00072 fixed; *R* -factor 0.064; *wR* 0.061; absorption corrections were not applied.

The structure was solved using direct-methods and difference-Fourier syntheses. Blocked-cascade least-squares refinements (SHELXTL[136]) were employed, with reflection weights $1/[\sigma(F)+g\,(F^2)]$. The function minimized was $\Sigma w\,(|Fo| - |Fc|)^2$. Anomalous dispersion corrections were from Cromer and Liberman.[137]

Methyl hydrogen atoms were included as rigid groups pivoting about their carbon atoms. All non-hydrogen atoms were assigned anisotropic temperature factors.

Final Fourier syntheses showed no significant residual electron density and there were no abnormal discrepancies between the observed and calculated structure factors.

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Crystallography;

3,4,5-Trimethyl-2-nitro-4-hydroxy-6-phenylcyclohexa-2,5-dienone (120): Crystal unit cell data were measured accurately using a Nicolet XRD P3 four-circle diffractometer and are given below. The space group was determined unambiguously from the systematic absences (0kl, k+1=2n+1; h0l, h=2n+1;h00, h=2n+1; 0k0, k=2n+1; 00l, l=2n+1).

Molybdenum X-radiation from a crystal monochrometer [λ(MoKα) 0.71069 Å] and the $\theta/2\theta$ scan technique were used to collect reflection intensities at 173 K out to a maximum Bragg angle θ 26°. The cell parameters were determined by least-squares refinement using the setting angles of 25 accurately centred reflections ($28° \leq 2\theta \leq 30°$). Absorption corrections were not applied.

Crystal Data:

4-Hydroxy -4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120)

$C_{15}H_{14}NO_4$. *M* 272.27, orthorhombic, space group *Pna* 2_1, *a* 20.380(7), *b* 6.304(3), *c* 10.781(5) Å, *U* 1385.13 $Å^3$, D_m 1.29 g cm^{-3}, D_c 1.31 g cm^{-3}, Z 4, μ(Mo Kα) 0.89 cm^{-1}. The crystal was colourless and of approximate dimensions 0.1 by 0.46 by 0.4 mm. Number of independent reflections measured 1432, number with $I > 3\sigma(I)$ 551; maximum Bragg angle θ 26°; *g* 0.00106; *R* -factor 0.052; *wR* 0.060; absorption corrections were not applied.

The structure was solved using direct-methods and difference-Fourier syntheses. Blocked-cascade least-squares refinements (SHELXTL[136]) were

employed, with reflection weights $1/[\sigma(F)+g\ (F^2)]$. The function minimized was $\Sigma w\ (|Fo| - |Fc|)^2$. Anomalous dispersion corrections were from Cromer and Liberman.[137] Methyl hydrogen atoms were included as ridged groups pivoting about their carbon atoms. Final Fourier syntheses showed no significant residual electron density and there were no abnormal discrepancies between the observed and calculated structure factors.

Crystallography;

Trans-*9,10-dihydro-9-nitrato-10-nitrophenthrene (135):* Crystal unit cell data were measured accurately using a Nicolet XRD P3 four-circle diffractometer and are given below. The space group was determined unambiguously from the systematic absences (0kl, k+1=2n+1; h0l, l=2n+1; hk0, k=2n+1). Molybdenum X-radiation from a crystal monochrometer [λ(MoKα) 0.71069 Å] and the ω scan technique were used to collect reflection intensities at 183 K out to a maximum Bragg angle θ 26°.

The cell parameters were determined by least-squares refinement using the setting angles of 25 accurately centred reflections ($28° \leq 2\theta \leq 30°$). Absorption corrections were not applied.

Crystal Data:

Trans-9,10-dihydro-9-nitrato-10-nitrophenanthrene (135) $C_{14}H_{10}N_2O_5$, *M* 262.24, orthorhombic, space group *P mmm*, *a* 9.473(3), *b* 14.361(4), *c* 19.024(5) Å, *U* 2588 Å^3, D_m 1.45 g cm^{-3}, D_c 1.47 g cm^{-3}, Z 8, μ(Mo Kα) 1.1 cm^{-1}. The crystal was colourless and of approximate dimensions 0.56 by 0.44 by 0.6 mm. Number of independent reflections measured 2897, number with $I > 3\sigma(I)$ 1468; maximum Bragg angle θ 26°; *g* 0.00067; *R* -factor 0.041; *wR* 0.050; absorption corrections were not applied.

The structure was solved using direct-methods and difference-Fourier syntheses. Blocked-cascade least-squares refinements (SHELXTL[136]) were employed, with reflection weights $1/[\sigma(F)+g\ (F^2)]$. The function minimized was $\Sigma w\ (|Fo| - |Fc|)^2$. Anomalous dispersion corrections were from Cromer and Liberman.[137] Methyl hydrogen atoms were included as ridged groups pivoting about

their carbon atoms. All non-hydrogen atoms were assigned anisotropic temperature factors. Final Fourier syntheses showed no significant residual electron density and there were no abnormal discrepancies between the observed and calculated structure factors.

Table A.1 Fractional coordinates for the atoms in 3,4,5-Trimethyl-4'-nitrobiphenyl (98), $C_{15}H_{15}NO_2$. The equivalent isotropic temperature factor is defined as one-third of the trace of the orthogalized U Tensor.

Atom	10^4X/a	10^4Y/b	10^4Z/c	10^3U
C(1)	6704(9)	7821(4)	848(5)	24(2)
C(2)	6192(9)	8757(4)	859(6)	29(2)
C(3)	6165(9)	9268(4)	1853(6)	33(2)
C(4)	6631(9)	8838(4)	2843(6)	33(2)
C(5)	7196(9)	7899(4)	2842(5)	32(2)
C(6)	7209(9)	7420(4)	1849(5)	29(2)
C(7)	6684(10)	7280(4)	-189(6)	28(2)
C(8)	6230(9)	6324(4)	-161(5)	27(2)
C(9)	6115(10)	5805(4)	-1118(6)	36(3)
C(10)	6480(10)	6222(4)	-2097(5)	32(2)
C(11)	6981(9)	7156(4)	-2188(5)	34(2)
C(12)	7040(9)	7668(4)	-1224(5)	29(2)
C(13)	5634(11)	10289(4)	1800(6)	43(3)
C(14)	6587(12)	9375(4)	3947(6)	44(3)
C(15)	7745(13)	7410(5)	3902(6)	49(3)
N(1)	6357(8)	5672(4)	-3126(5)	43(2)
O(1)	5876(8)	4854(3)	-3053(4)	57(2)
O(2)	6719(8)	6039(3)	-4020(4)	60(2)

Table A.2. Fractional coordinates for the atoms in 4-Hydroxy-3,4,5-trimethyl-2-nitro-6-phenylcyclohexa-2,5-dienone (120) $C_{15}H_{14}NO_4$. The equivalent isotropic temperature factor is defined as one-third of the trace of the orthogalized U Tensor.

Atom	10^4X/a	10^4Y/b	10^4Z/c	10^3U
O(1)	4964(4)	4996(11)	9256	26(2)
O(4)	4624(3)	1022(10)	4923(9)	23(2)
O(21)	3441(3)	5824(11)	8046(9)	38(2)
O(22)	3587(3)	3595(10)	9543(9)	36(2)
N	3712(4)	4301(13)	8523(10)	28(2)
C(1)	4916(4)	3906(15)	8303(10)	22(2)
C(2)	4269(4)	3287(15)	7833(12)	21(2)
C(3)	4144(4)	2040(15)	6877(11)	21(3)
C(4)	4730(4)	969(17)	6246(12)	24(3)
C(5)	5384(4)	1896(14)	6591(11)	17(2)
C(6)	5477(4)	3173(15)	7592(11)	17(2)
C(7)	3469(4)	1595(17)	6395(11)	32(3)
C(8)	4726(5)	-1393(15)	6622(12)	31(3)
C(9)	5961(4)	1226(16)	5791(11)	28(3)
C(61)	6139(4)	3880(15)	8013(11)	17(2)
C(62)	6400(5)	5839(18)	7643(12)	36(3)
C(63)	7012(5)	6492(17)	8085(12)	38(3)
C(64)	7356(5)	5252(16)	8894(11)	32(3)
C(65)	7105(5)	3356(17)	9278(13)	40(3)
C(66)	6485(4)	2672(17)	8824(11)	29(3)

Table A.3. Fractional coordinates for the atoms in *trans*-9,10-Dihydro-9-nitrato-10-nitrophenanthrene (135) $C_{14}H_{10}N_2O_5$. The equivalent isotropic temperature factor is defined as one-third of the trace of the orthogalized U Tensor.

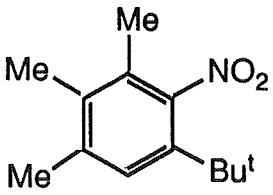
Atom	10^4X/a	10^4Y/b	10^4Z/c	10^3U
O(91)	744(2)	623(1)	1499(1)	29(1)
O(93)	-774(2)	1328(1)	2167(1)	43(1)
O(92)	1174(2)	840(1)	2648(1)	42(1)
O(11)	3488(2)	-2094(2)	1541(1)	65(1)
O(12)	4321(2)	-853(2)	2001(1)	47(1)
N(9)	363(3)	955(2)	2171(1)	33(1)
N(10)	3356(2)	-1312(2)	1747(1)	36(1)
C(1)	-38(3)	-2021(2)	1554(1)	30(1)
C(2)	-1001(3)	-2484(2)	1127(1)	33(1)
C(3)	-1003(3)	-2313(2)	409(1)	33(1)
C(4)	-71(3)	-1681(2)	118(1)	28(1)
C(4a)	890(3)	-1196(2)	538(1)	22(1)
C(4b)	1877(2)	-492(2)	245(1)	23(1)
C(5)	2208(3)	-444(2)	-468(1)	28(1)
C(6)	3133(3)	224(2)	-723(1)	32(1)
C(7)	3749(3)	857(2)	-268(1)	33(1)
C(8)	3426(3)	826(2)	443(1)	30(1)
C(8a)	2499(3)	158(2)	700(1)	24(1)
C(9)	2121(3)	144(2)	1468(1)	25(1)
C(10)	1892(3)	-848(2)	1730(1)	28(1)
C(10a)	891(3)	-1379(2)	1262(1)	26(1)

Appendix (B)

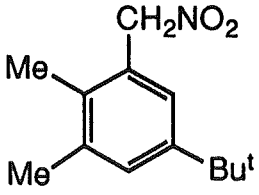
Attempted Reaction of 3,4,5-Trimethyl-5-X-benzene (X = OAc, Br, NO_2, CN, Bu^t) with Nitrogen Dioxide.

No reaction occurred when: 3,4,5-trimethylphenylacetate (155), 1-bromo-3,4,5-trimethylbenzene (156), 1,2,3-trimethyl-5-nitrobenzene (153), and 1-cyanio-3,4,5-trimethylbenzene (158) were treated with nitrogen dioxide. These results are in keeping with the known substituent effects of aromatic compounds with electrophilic reagents.[2]

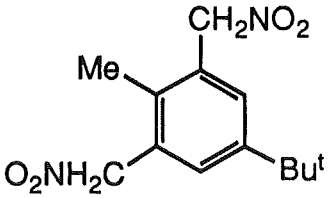
5-*t* -Butyl-1,2,3-trimethylbenzene (159) did react with nitrogen dioxide in benzene giving a complicated mixture containing three major products: nitro aromatic (161) (41%), nitromethyl aromatic (160) (13 %) and dinitromethyl aromatic (162) (5 %) (Figure B.1), in addition to a further nine minor products (total 32 %).



(161)



(160)



(162)

Figure B.1

Resubmission experiments showed that nitro aromatic (161) was unreactive, but the nitromethyl compound (160) reacted relatively slowly to give the dinitromethyl aromatic (162) and a large number of other products, which could not be separated.

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